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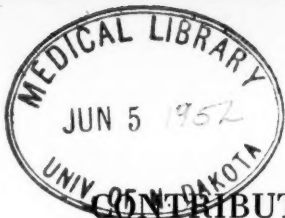
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SYMPOSIUM ON GASTRIC AND DUODENAL ULCER BEFORE THE CLINICAL SOCIETY OF THE LENOX HILL HOSPITAL, NEW YORK CITY

PARTICIPANTS

- I. A Few Remarks on the Medical Aspect of Gastroduodenal Ulcer. By JACOB KAUFMANN, M. D.
- II. x-Ray Findings. By WILLIAM H. STEWART, M. D.
- III. Surgical Aspect. By HERMANN FISCHER, M. D.
- IV. Pathologic Aspect. By GEORGE L. ROHDENBURG, M. D.

DISCUSSION

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I. A FEW REMARKS ON THE MEDICAL ASPECT OF GASTRODUODENAL ULCER

JACOB KAUFMANN, M. D.

THE most striking feature in ulcer discussion is the disagreement in matters of ulcer pathology. It reflects the lack of knowledge of the vital processes underlying the disease. Yet it stands to reason that the formulation of methods of treatment requires

not only a positive diagnosis of the presence of, but more urgently an understanding of the pathologic character of, an ulcer.

I shall present only a very brief outline of a general conception of ulcer pathology to serve the discussion of certain principles which I think should be made the basis for advising methods of treatment.

Gastroduodenal ulcer is usually considered a local disease. Although various methods of examination have uncovered many different types of disorder connected with the disease, none the less its etiology remains misty, its pathogenesis unexplained.

Giving only the headlines of groups of these disorders, I mention:

1. Disordered gastric circulation resulting from pathology of gastric arteries and other causes.
2. Blood dyscrasias.
3. Disorders of gastric secretion.
4. Disturbances of gastric motility.
5. Mechanico-functional conditions like the stomach-rod and the isthmus and other local disorders, such as inflammation, lymphoid hyperplasia, transformation of glandular cells.
6. Physical, chemical, thermic traumatism of the gastric wall.
7. Infection of various kinds.
8. Derangements of autonomic innervation and of endocrine activity provoked in many different ways.

At different times the one or the other of these disturbances has been marked as the primary cause. The stamping of just one disorder as the essential causative element has entailed a great deal of controversy and confusion, especially when the disorder is presented, as it is so often in a generalized way, as prevailing in every case.

Any one of the numerous disorders under the above grouping may be present in a given case. But none offers in itself a satisfactory solution for the clearing of the pathogenesis of gastro-duodenal ulcer. Whichever one is present acts merely as one factor among others. To establish the interrelation of the various disorders encountered in a given case we need a com-

prehensive viewpoint enabling us to give to each disorder its proper place in the field of pathogenesis.

Experiences of various kinds in the course of years have ripened in me a conception which has proved helpful in the study of ulcer pathology by providing such a comprehensive viewpoint. Loosely and briefly formulated, I present it as follows:

While gastroduodenal ulcer is morphologically localized, and while certain outer influences play a more or less important causative rôle in the development, none the less the origin, character, and course of the disease are in many ways determined by constitutional influences.

The introduction of the constitutional element into the query of pathogenesis by contrasting inner and outer influences offers a vantage ground from which we may evaluate the meaning and importance of any causative factor, thus opening up a wider avenue of approach for the study of the deeper causes of the disease.

This is the problem which will have to be solved at least to a certain degree before we may hope to fathom the vital processes underlying the disease. The task is difficult partly due to the fact that so many of the technical terms in daily use in ulcer questions are ill defined and carry faulty meanings.

Let me take up just one point to show to what extent erroneous conceptions may prove misleading. To illustrate, I pick out Moynihan's once famous dictum: "Every chronic hyperchlorhydria means chronic duodenal ulcer." Without wishing to detract from Moynihan's great merit in promoting knowledge of duodenal ulcer, it must be stated that Moynihan, in this one short sentence, interlinked two theoretic errors.

What Moynihan had in mind when he coined the terse yet confusing statement was the hunger pain so often observed in ulcer patients. He himself made that clear in other statements, which summarized, read: "To diagnose duodenal ulcer it is not necessary that any examination of the patient be made; the hunger pain is sufficient evidence."

For so long a period of time it had been customary to attribute to hyperchlorhydria the occurrence of pain, that hunger

pain and hyperchlorhydria are considered as synonyms, and that No. 1 is used to prove the presence of No. 2 and No. 2 is used to prove that an ulcer is present.

What, precisely, are the facts of the matter?

In the first place, the regular occurrence of hunger pain is observed in patients when no ulcer is present, as demonstrated by negative findings at operations purposely undertaken for dealing with an assumed ulcer. In the second place, it has been claimed, but has never been proved, that acidity as such provokes pain. We often find very high gastric acidity figures when no pain is noted, and we may meet the characteristic hunger pain in patients with complete lack of gastric secretion.

A year ago the English internist, Hurst, reporting a series of cases in which visual inspection had shown an ulcer while gastric analysis revealed achylia gastrica, proposed on that account to abolish altogether the term "peptic" ulcer as unjustified and misleading. At about the same time the surgeon, Crile, started a paper with this sentence: "Hypersecretion of acid is the central figure of, if not the actual cause of, peptic ulcer." On the strength of this conception, he advocates the extensive gastric resection as first practised by Haberer, Finsterer, and Moynihan, and in our hospital by Dr. Fischer and others. At a meeting of the German Medical Society recently you heard Dr. A. A. Berg utilize the same argument in his plea for doing subtotal gastrectomy in all ulcer cases. It is true that Dr. Berg referred also to the factor of inflammation. Time permitting, I could refute his argumentation on the score of that factor.

Instead, let me say a few words about another of Dr. Berg's statements, which contains in a nutshell the error usually indulged in when discussing ulcer treatment. Dr. Berg said, "By medical treatment you heal an ulcer, while by subtotal gastrectomy I cure the patient of his disease."

To avoid misunderstanding, I declare that I am not against operation. I merely militate against its indiscriminate employment. Especially against basing a generalized indication for doing subtotal gastrectomy in all ulcer cases upon so uncertain

a ground as that furnished by unproved theories, like that of the paramount causative influence of secretory disorders, or by the overvalued importance of the inflammatory element.

In certain cases during the course of the disease local conditions may arise which may call for operative measures. Such possibility was clearly perceived and described by an internist long before abdominal surgery became a reality. In 1869, in his classic treatise on treatment of gastric dilatation by lavage Kussmaul so well defined some of the principal indications for surgical interference that they are still valid.

In the main the object of surgery is to deal with structural products of the ulcerative process, especially with scar tissue causing obstruction or acting as a source of irritation and preventing the healing of an ulcer. To that extent we may consider surgical measures as causal methods of treatment. They do not, however, reach the deeper causes of the disease, and are especially ineffective in combating the constitutional influences. For this reason there is no justification for generalizing on the indication of any method of operation. On the contrary, the indication for operating should be worked out separately in each concrete case under full consideration of all conditions connected with the case.

For years I have, with such cases, followed the habit of putting before the patient all pros and cons and have let him decide the issue for himself. This became my habit through the frequent experience I had in former years, that patients whom I had urged to undergo operation, either left me to seek medical treatment elsewhere or they persuaded me to try medical treatment while relieving me of all responsibility in case of failure. These people reason that it might be just their hard luck to become one of the so-and-so-many percentage of operative mortality, be that ever so small, and prefer to be 50 per cent. alive, with periodical suffering, than to be 100 per cent. dead. In not a few of these cases when they stayed with me I have been surprised to see structural conditions change and improve, which at the start of the treatment I had looked upon with great suspicion. Among my records of such cases are those of phys-

icians and even that of a surgeon. Other ulcer patients of this group feel differently: they wish to be relieved of suffering which mars their lives, but not being willing, or being unable for one reason or another to pursue tedious medical methods of treatment, are ready to take their chances, in which event I encourage the decision in favor of operation.

Now for this group of cases in which the previous conservative methods of operating have proved just as often a failure in regard to final results as did medical methods of treatment, subtotal gastrectomy is recommended as promising considerably better end-results. That may prove true for certain cases, but whether it actually cures a patient of the *ulcer disease*, as claimed by Dr. Berg, remains to be seen. I am ready to be convinced when shown. I confess, however, to harboring doubts aroused by my conception of ulcer pathology. A patient who survives subtotal gastrectomy is still the same person, constitutionally predisposed to develop under the influences of life the same systemic derangements which provoked the ulceration in the first instance. There still remain part of the stomach and an opening into the gut, and who will venture to predict what is going to happen when the patient is once more constitutionally upset?

I admit the possibility that the removal of the greater part of the stomach with the consequent elimination of its activity may exert a beneficial effect on the constitutionality of a person, similarly to the effect of thyroidectomy in certain cases of Graves' disease. But even if this should prove to be the case, it would constitute no argument for having all ulcer cases undergo the after-all hazardous subtotal gastrectomy, and thereby—in case of survival—deprive a person of a stomach the activity of which in many cases may be subdued by simpler and less dangerous means.

The cases referred to as having developed such structural conditions that may call for surgical interference represent only a certain percentage of all ulcer cases. The experience of forty years of active practice has convinced me of this fact.

In the vast majority of cases the ulcer disease is of milder

character, and with many of them remains so even if running over longer periods of life. Of this larger group it may truly be said, ulcers come and ulcers go. They have a natural tendency to heal if given a chance and if not unnecessarily interfered with. This is partly the reason why so many different methods of treatment, medical as well as surgical, yield a good immediate result in a high percentage of cases. Neither of the standardized methods of treatment, however, has any effect in preventing recurrences, if we except, for the moment, subtotal gastrectomy.

If you wish to prevent recurrences—without resorting to subtotal gastrectomy—you will have to study your patient's constitutional make-up and its shortcomings, and then teach your patient the art of living. A difficult task, but worth while.

It is not stretching imagination too far when we expect that individualized treatment, based on the understanding of the constitutional element, will probably reduce the number of those cases which incline to develop in the course of the disease the more severe conditions, similarly to the experience we had in tuberculosis, diabetes, Graves', and other chronic diseases, in the development of which the constitutional element strongly predominated. Once you free yourselves of erroneous conceptions of ulcer pathology and approach your patients with an open mind, you will learn to appreciate this outlook.

II. X-RAY FINDINGS

WILLIAM H. STEWART, M. D.

My part of the subject of this symposium will deal entirely with x-ray findings in gastric and duodenal ulcer. I believe the value of the Roentgen examination in the diagnosis of gastric and duodenal ulcer has not been fully recognized, and I believe the percentage of recognition of these lesions is from 85 to 90 per cent. A slight amount of erosion of the gastric wall may, in some patients, be difficult to recognize by means of the x-ray, but usually in these early cases there are secondary signs, such as spasm and tenderness, even though no defect is actually

present which enables us to recognize the lesion. Certainly the x-ray does not always coincide with the string test. Very frequently a case with a positive string test will not show x-ray evidence of an ulcer. In fact, it is not unusual to find a positive string test in a flabby, enlarged stomach which shows absolutely no defects, tenderness, or spasm. In this class of cases I hesitate always to accept the diagnosis of ulcer, even though there is "a stain upon the string." The x-ray is, of course, most positive in penetrating and perforating ulcers. There we feel so confident that I believe our percentages can go almost as high as 100 per cent. provided the examination is carefully made and the posterior and anterior surfaces, as well as the tube, covered.

III. SURGICAL ASPECT

HERMANN FISCHER, M. D.

It is a great pleasure for me to say a few words this evening about the surgical treatment of ulcer of the stomach and the duodenum.

As the allotted time is very limited I shall confine myself only to the more important points—the indications for operation and the choice of the operative procedure. The indications for surgical intervention in gastric and duodenal ulcer, as I conceive them today, are as follows:

1. Patients who have been treated medically by competent men and who have gone through one or more ulcer cures without becoming free of symptoms should be operated upon. *To continue medical treatment for years with the only result of alleviating symptoms for a shorter or longer period, exposing the patients to the danger of hemorrhage, perforation, and possible malignant degeneration, is today not justified.

2. Symptoms of pyloric obstruction not relieved by medical treatment.

3. Repeated hemorrhages (hematemesis and occult hemorrhages).

4. The penetrating type of ulcer.

5. Perforation an absolute indication.

If we have decided in a given case that surgical treatment should be resorted to, the important question arises which of the many operations that have been devised should be used. I would like to state here that there is no standard operation that could be employed in every case, and that I approach every case as a case for an exploratory laparotomy, the mode of procedure to be decided upon after the abdomen has been opened and the diseased parts have been carefully inspected.

A great many methods are at our disposal. I shall divide them into conservative operations and radical operations.

The conservative operations are:

1. Gastro-enterostomy.
2. The different methods of plastic operations.
3. The local excision of the ulcer with or without gastro-enterostomy.

The radical procedure is resection of the stomach, including resection of the pylorus.

For almost forty years gastro-enterostomy was the operation of choice for duodenal ulcer, pyloric ulcers, and for those ulcers at the lesser curvature which were situated in the vicinity of the pylorus whether on the anterior or posterior portion, whether penetrating or not.

Gastro-enterostomy was first devised by Woelfler in 1881 as a drainage operation in cases of pyloric obstruction. Doyen in Paris in 1883 was the first surgeon to use and advise gastro-enterostomy for the cure of pyloric ulcer. Since that time this operation has been taken up by all surgeons as a standard operation for the cure of gastric and duodenal ulcers, and seemingly with satisfactory results.

There is no question about it, and the experience of many surgeons the world over has proved that gastro-enterostomy, if properly performed and used in proper cases, will cure a large number of gastric and duodenal ulcers. Statistics in the various large clinics vary between 70 and 90 per cent. cures. The immediate result of gastro-enterostomy is often very striking, especially upon the pain which is caused by pylorospasms. This painful pylorospasm is often of such severity that it may be

confounded with a gall-stone colic or a renal colic. After gastro-enterostomy this pain is relieved in a large percentage of cases almost immediately after operation. Besides gastro-enterostomy, several other operations of the conservative type are in use. I refer to the gastroduodenostomy after Finney and Horsley's pyloroplasty with or without excision of the ulcer. Both these operations have been used with more or less good results in duodenal ulcers, ulcers at the pylorus, and in pyloric stenosis. In pyloric stenosis due to scar contractions Finney's operation should have been the preference to gastro-enterostomy if the duodenum can be mobilized. It seems a more physiologic operation and avoids the danger of a jejunal ulcer. In small ulcers of the lesser curvature which are situated distant from the pylorus or high on the lesser curvature, cautery excision after Balfour may be practised.

As the years passed by it was found by the medical men, as well as by the surgeon, that not a small percentage of patients in whom a gastro-enterostomy or one of the other conservative operations was performed did not do so well as was expected. After a certain period of health these patients again complained of pain, of nausea, and hyperacidity. Some even experienced more or less severe hemorrhages and even were the unfortunate victims of perforation of the ulcer, or they developed a peptic ulcer either at the anastomosis or in the jejunum. These failures of the conservative operations to cure permanently have prompted many surgeons of large experience to turn to the radical operation, namely, resection of the ulcer-bearing portion of the stomach.

In my own work I have had similar experiences which have led me to adopt a more radical attitude toward gastric and duodenal ulcer, and for the last ten years the operation of choice in my material has become the resection of the ulcer-bearing portion of the stomach together with the pylorus and antrum. I restrict gastro-enterostomy to such cases in which resection is contraindicated on account of the poor condition of the patient or insurmountable operative difficulties. If we resect the ulcer-bearing portion of the stomach it is of importance to resect

the pylorus and the antrum so that about a little more than one-third of the stomach is sacrificed. Modern physiologic teachings have shown that the acid-producing glands which are situated in the fundus of the stomach are stimulated by a hormone secreted by the glands of the pyloric region. If, therefore, the pylorus and the antrum of the stomach are removed we influence the production of HCl. It is a fact that after resection of these parts of the stomach a long standing hypo- or even anacidity can be produced, which protects the patient against ulcer recurrence in the stomach and against the formation of a jejunal ulcer.

Several methods are at our disposal to restore the continuity of the alimentary tract after resection of the stomach, namely, end-to-end anastomosis of stomach and the duodenum according to Billroth's Method I, or the posterior gastro-enterostomy with the rest of the stomach, Billroth's Method II. There are in existence today a number of the modifications of the Billroth Method II, of which I prefer the end-to-end antecolic anastomosis of stomach and jejunum with long jejunal loop.

In duodenal ulcer I prefer also resection of diseased area with removal of one-third of stomach if the condition of the patient allows it and the duodenum can be sufficiently mobilized without getting into conflict with the bile-ducts.

According to my personal experience in the last ten years since I have practised resection in preference to gastro-enterostomy in gastric and duodenal ulcer, I have gained the impression that the radical procedure gives the best end-results. The number of my cases, however, is too small to draw fixed conclusions from my own work, but the reports of other surgeons, in Europe and here, with larger material seem to support my own experiences. The immediate mortality of gastric resection is about 5 to 7 per cent., the immediate mortality of gastro-enterostomy 2 per cent., but there is a remote mortality of gastro-enterostomy from hemorrhages after operation and from perforation which is given as 5 to 15 per cent., and so, after all is said and done, the total mortality after resection is much smaller in comparison and the end-results infinitely better.

Everyone of my resected cases which I could follow since

1914 has had no disturbances, is able to work, and can eat everything without paying attention to the diet sheet.

IV. PATHOLOGIC ASPECT

GEORGE L. ROHDENBURG, M. D.

THE pathology of gastric and duodenal ulcer can be divided into sections. One section concerns the local condition of the ulcer of the stomach or duodenum, and of this phase we know much. The other phase concerns that vague something, termed "constitutional predisposition," of which we know very little.

The varied positions of the ulcer in the stomach and duodenum have been shown by Dr. Stewart's slides. To refresh your memories, I have here a picture of a specimen of a typical perforating ulcer of the stomach and a microphotograph of the same lesion.

Ulcer of the stomach or duodenum may be of varying degree, as one might say. Slight erosions of the mucous membrane are common, occurring after periods of vomiting, with chronic congestion, as in the congestions which occur in nephritis and in cardiac lesions. Similar lesions also occur in some of the acute infectious diseases. In earlier years ulcer was thought to be an embolic process. With abrasions and small ulcers, common as they are, the strange thing is that so many of them heal and so relatively few fail to heal, the latter producing the type of ulcer with which the physician and surgeon come so often in contact. The tendency of the ulcer to heal or to recur repeatedly is apparently dependent upon this vague something called constitutional predisposition. Doctor Kaufmann has explained his views.

Our work has not been as extensive as that of many others, but investigation has shown that a good many of the gastric ulcer cases have had symptoms referable to the appendix or the gall-bladder before the occurrence of the ulcer symptoms.

In these appendices and gall-bladders we have been able to demonstrate lesions of the ganglion-cells of Auerbach and Meissner's plexuses. It seems reasonable to suppose that such

lesions are not restricted to the gall-bladder or appendix alone, but are to be found throughout the gastro-intestinal tract. Possibly a lesion of this sort might explain the etiology of gastric and duodenal ulcer. The specimen here presented seems to bear out a nerve etiology, for it is a perforating gastric ulcer at the pylorus of a rabbit, occurring two months after bilateral resection of the vagi. The good results obtained by Dr. Fischer are possibly explainable also on the same basis, for in the operation advocated by him there is coincidental section of the nerve supply of the stomach. This and not the removal of the acid-producing glands may be the explanation of the good result.

There is still a wide field for investigation, notably in view of the present confusion of the sympathetic nervous mechanism of the stomach and its relation to secretion, motor activity, and spasm.

DISCUSSION

MAX EINHORN, M. D.

I WAS very much interested in the papers read and I agree with Dr. Kaufmann that a great many ulcers can be cured and that not all of them should be treated in the same way. They have an individuality.

With regard to Dr. Stewart's remark that about 95 per cent. can be proved radiographically with positive findings for gastric and duodenal ulcer: this is of great importance, but I think in the frequency of these proofs the percentage is not so high, and I think we can show the presence of ulcer by other methods where the x-ray fails and where the symptoms indicate that an ulcer is present.

With regard to the curability of these ulcers, Dr. Fischer included a category for certain penetrating ulcers as belonging definitely to the surgeon, and I would like to say that my experience does not tally with that. That is to say, I have seen a great number of such cases of distinct penetrating ulcers that have been cured as far as I can see radiographically and also symptomatically, *i. e.*, cured of their symptoms.

With regard to total resection or subtotal resection I would compare it with, let us say, a simple ulcer of the leg. Can you cure the ulcer if you cut off the leg, and can you say that the ulcer is cured by that means? This is similar to saying that you can cut off part of the stomach, and the ulcer is cured. But is that a cure?

When the first operation for removal of the stomach was done by Schlatter for cancer of the stomach there was an excuse for it. We know that a man with cancer cannot live. If you can succeed in cutting away the stomach of such a man so that he may live—that is one thing; but to take away a stomach, a useful organ, and say, "Here we have cured an ulcer," and an ulcer that might very well have been cured entirely without so radical a procedure—is another. Besides, the mortality is quite great. Berg says he has a mortality of 5 to 6 per cent. He is very expert and has been following this procedure for a long time. Other surgeons, not so experienced, have a higher mortality. If the percentage of mortality under gastro-enterostomy is higher than is at first supposed, because the patients sometimes die from recurrent ulcer, at least these patients have lived meanwhile, while the other patients who have succumbed to stomach resection have died.

With an extensive penetrating ulcer the question is somewhat different. I had a patient whom Dr. Rafsky and I treated together; the patient had hemorrhages, lost greatly in weight, and we were both of the opinion that he should be operated on. When I told the patient this opinion he said he would rather die than submit to an operation. We then decided to try a certain treatment, and did so, and, contrary to our prediction, he got better and better. The penetrating ulcer disappeared altogether, and it was a big one, the largest I have ever seen. He is alive today, although that was three or four years ago. He is an old man, and if he lives another year I think we shall be satisfied. I think anybody should be satisfied to die at the age of seventy-seven.

O. HENSEL, M. D.

It is rather difficult to take part in this personal battle between internist and surgeon in so short a space as five minutes. I think one of the reasons why there are so many symposiums on ulcer is because it always means a fight, and most of us like a fight. It is interesting to contrast the ulcers we saw when I was intern at the hospital twenty-five years ago. In those days most of the cases were young girls suffering from chlorosis, and, like chlorosis itself, this type of disease seems to be dying out. Of course, we did not have the x-rays and did not so regularly practice stool examination, so that probably many of the cases were not real ulcer, but gastropptosis, gall-bladder disease, endocrine disturbances, etc. Yet a large number of real cases remained and in these the treatment was usually very simple. They got well with a simple diet; alkalies and measures directed toward their anemia and surgery would rarely have been necessary even if it had advanced to the present state. The disappearance of these ulcers is no doubt due to a better understanding of hygiene, to better attention to the teeth, more frequent tonsillectomies, and, in general, better living conditions among the female sex. The fact that we have fewer recent immigrants may play an important rôle, for hygiene is not so generally practised in Europe as here. We may truly say that the labor laws have helped us to conquer one type of disease.

The ulcers we see today are more common in men in advanced life and involve the stomach or duodenum. It is surprising how common this disorder is; there are times when as high as 20 per cent. of our admissions on the medical service are ulcers. These men have not had the advantages of modern life; they smoke a good deal, use boot-leg liquor, and do not have their tonsils and teeth attended to as do the young people of today.

The medical treatment of uncomplicated ulcer is a very simple matter. It makes very little difference whether you treat according to Leube, Senator Lenhartz, Einhorn, Sippy, or use any of the other methods or stunts that have been recommended. These patients promptly lose their pains and can usually be

discharged after one week of orientation and two weeks of rest in bed. But all we medical men realize that when it comes to preventing recurrences the results are very disappointing. We thus found in all our admissions during the last six months that as high as 80 per cent. of the patients gave a history of previous attacks. With private patients the problem may be simpler, for we can supervise their diet and their mode of life in many instances, but with the ordinary ward case no amount of social service work will accomplish this. These patients again return to their former bad habits, finally get tired of returning to the hospital, and of their own accord may demand an operation. It is thus necessary for the medical man to realize that there are indications for surgery even in the uncomplicated ulcer.

I have two criticisms to make of the surgeon: one, that he often does not realize that the case is still a medical case, and that when he is finished with his task he should return the patient to the medical man, for proper medical treatment is just as important after operation as before. The second criticism is that in his praiseworthy attempt to cure the patient the surgeon often finds it necessary to perform so extensive an operation that not all recover.

I would say, therefore, in conclusion, treat your cases medically whenever possible. It makes little difference what method you use; the results are good with all. If you get relapses which you cannot prevent, send your patient to the surgeon, but do it with a little prayer that the surgeon may let you have the patient again, and that he may be as quick and as conservative in his operation as his conscience will permit.

GEORGE L. LAPORTE, M. D.

I agree fully with Dr. Kaufmann's idea that in gastroduodenal ulcer a constitutional predisposition, let us call it ulcer sickness with Dr. Kaufmann, or ulcer diathesis, as it has been called by H. Straus, is a factor of prime importance. That is one of the reasons why the disease has a tendency to recur and why so many surgically treated cases have to be taken again in hand later on by the internist. During the last

ten years I have never recommended an operation for duodenal ulcer to any patient under thirty-five years of age. In Montefiore Hospital I have seen a great many bad results from young patients who had been operated for duodenal ulcer. All of them were under twenty-five years of age, some of them with three or four scars on their abdomen. They were suffering more from the adhesions than from any new ulceration, and they were physical wrecks. As Dr. Einhorn has remarked, it is not even necessary to operate in all cases of pyloric obstruction, as quite a number of the less severe cases get well with medical treatment. I am not now discussing perforated ulcer, that is of course a surgical condition for which there is no other treatment, but we gastro-enterologists see very few of them, as they are usually treated by the family physician.

In gastric ulcer the conditions are somewhat different, as surgical treatment is here more frequently indicated than in duodenal ulcer. Twenty years ago gastric ulcers were much more frequent or at least more often diagnosed than duodenal conditions. Duodenal ulcer was then a medical curiosity, the chief predisposing causes being then given as skin burns, and that it was particularly liable to attack cooks. I do not know whether they were in reality less frequent then or whether prohibition and the drinking of all kinds of home-made concoctions has had anything to do with the marked increase in frequency of duodenal ulcer during the last six years. At all events, it is a fact that we treated a great many more gastric ulcers at that time than now. They occurred usually in young girls and got well under appropriate medical treatment, being the acute type of ulcer that has a marked tendency to heal. With chronic gastric indurated ulcer the condition is a little more difficult. Here always the question of cancer developing on the basis of the ulcer comes up. It is a pathologic rarity to have duodenal ulcer turn into cancer. Cancer may, however, develop upon the base of a gastric ulcer. That it does develop to the extent that earlier reports from surgical clinics of Europe and America (some statistics being as high as 60 per cent.) would seem to indicate has, I believe, been disproved of late

by pathologists, internists, and even surgeons. In this connection I would like to call attention to the interesting investigations of Anachuetz and Konyetzny, who tackled this problem in a new fashion. They followed up the history of about 500 patients who had been operated for ulcer, and found that $3\frac{1}{4}$ per cent. later developed carcinoma. They were very careful to be sure that it was really a cancer engrafted upon an old ulcer and not merely a cancer that had broken down and become an ulcer. This possibility of the development of cancer on a gastric ulcer must, of course, incline us more frequently to the advisability of surgical intervention.

Now as to the statement of Dr. Stewart that ulcer can be diagnosed in 95 per cent. of the cases merely by the *x*-ray findings, I am compelled to take exception. I am very glad to acknowledge that the development of *x*-ray technic has greatly aided us in the diagnosis of duodenal ulcer and that the percentage of correct *x*-ray diagnoses is greater in duodenal than in gastric ulcer. In the latter condition, to my mind, it will fail to demonstrate the presence of an ulcer, undoubtedly present, in a somewhat greater proportion of cases than Dr. Stewart claims. Especially is this so in the acute type. We all talk readily of niches and incisures; niches are more frequent, but incisures, the second cardinal *x*-ray sign of a gastric ulcer, are much rarer. Also I do not believe that roentgenologists can always clearly differentiate between an open, unhealed duodenal ulcer and one that has healed, and shows only the after-effects of this, like scarring and adhesions.

A. L. GARBAT, M. D.

In the medical treatment of gastric and duodenal ulceration one of the basic principles has been to put the stomach at rest as much as possible from its motor activity as well as from its secretory action. It was primarily to carry out this object that the method of duodenal feeding over an extended period of time was proposed and carried out by Einhorn and his school. By the concomitant use of two duodenal tubes, one in the duodenum and the other in the stomach, the writer, however, showed

that gastric secretion and consequently gastric motor activity could not be eliminated by duodenal alimentation alone. It was found that a definite cycle of gastric secretion starts just as soon as food enters the duodenum and continues for some time after.

The amount of gastric juice secreted depends upon the type of patient dealt with, and compares very closely to what the gastric secretion would be in that same patient in response to the gastric test-meal. Thus, a patient with an achylia gastrica shows no gastric secretion in response to duodenal feeding. A patient with a mild irritative form of gastric disorder offers a moderate amount of gastric secretion—about 100 c.c., while patients with marked irritative form of gastric function, as cases of alimentary hypersecretion, give as much as 286 c.c. of pure gastric juice in response to a duodenal feeding (Chart I).

CHART I

GASTRIC JUICE AFTER DUODENAL FEEDING WITH MILK-EGG MIXTURE—
10.13 STOMACH EMPTY; DUODENAL FEEDING STARTED AND CONTINUED
UNTIL 10.35

	Quantity of gastric secretion aspirated.	Free hydro- chloric acid.	Total acidity.
10.13 to 10.15 (first 2 minutes)...	48 c.c.	36	50
10.15 to 10.25 (next 10 minutes)...	50 "	76	88
10.25 to 10.35	50 "	56	70
10.35 to 10.45	30 "	46	58
10.45 to 11.00	50 "	48	68
11.00 to 11.15	38 "	54	68
11.15 to 11.30	15 "	60	70
11.30 to 11.45	5 "	4	20
Total	286 "		

The amount of instigated gastric secretion also differs with different food substances that are injected into the duodenum. Most of the tests were done with duodenal alimentation consisting of a mixture of 7 ounces of milk, 2 eggs, $\frac{1}{2}$ dram of lactose, one square of butter, and a pinch of salt.

Experiments with different types of feeding undertaken in the same person were very striking. In a patient with a gastric ulcer and alimentary hypersecretion, comparative experiments, after individual feedings with 8 ounces of saline, 8 ounces of beef broth, 8 ounces of milk-egg mixture, and 8 ounces of thick, strained oatmeal gruel, showed the least amounts of gastric secretion, that is, 100 and 138 c.c. following the saline and the broth respectively; the greatest amount (377 c.c.) was stimulated by the 8 ounces of gruel, while the milk-egg mixture gave 286 c.c. (Chart II).

From repeated experiments with similar results this difference was explained by the finding that the longer the feeding remained in the duodenum as evidenced by aspiration, the longer did the gastric secretion continue. In all the tests, as soon as the duodenum became empty, the gastric secretion practically ceased. The saline and broth passed out of the duodenum most quickly, while the gruel stayed longer than the milk-egg mixture.

The mechanism concerned in this phenomenon may depend upon several factors. Although secretion continued as long as food substances remained in the duodenum, this was not caused by a simple distention of the duodenal loop. It may be due to a local secretory reflex from the intestinal mucosa to the gastric mucosa. On the other hand, it may be a long reflex to the cerebral centers, and a centrifugal response with either a secretory or vasomotor effect. The possible stimulation by secretin produced in the intestinal mucosa must also be considered, although the almost immediate appearance of the gastric secretion after the duodenal feeding, as is regularly noticed in the human being, without a latent period, speaks somewhat against the hormone element. The possibility of a psychic factor in influencing the results is, of course, always to be kept in mind.

Gastric secretion following duodenal alimentation can, however, be almost entirely eliminated if in addition to the duodenal feeding antacids or alkalies are administered by mouth just before each duodenal feeding. If the alkali or antacid is given after the completion of the duodenal feeding the cycle of gastric

CHART II
GASTRIC SECRETION AFTER DUODENAL ULCER FEEDING WITH VARIOUS SUBSTANCES

Time of aspiration after starting duodenal feeding.	Normal saline (8 ounces).			Beef broth (8 ounces).			Milk-egg mixture (8 ounces).			Thick oatmeal gruel (8 ounces).		
	Quantity of aspirated gastric secretion.	Free ¹ HCl.	Total ² acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.
15 minutes.	70 c.c.	22	38	90 c.c.	44	53	98 c.c.	51	69	175 c.c.	54	62
30 "	30 "	36	41	30 "	52	62	80 "	51	64	110 "	54	62
45 "	Duodenum	empty.	"	18 "	52	60	50 "	48	68	35 "	52	62
60 "	"	"	"	Duodenum	empty.	"	38 "	54	68	25 "	54	66
75 "	"	"	"	"	"	"	15 c.c.	60	70	25 "	74	78
90 "	"	"	"	"	"	"	5 "	4	20	Duodenum empty.	32	20

¹ As determined by titration with tenth-normal NaOH per 100 c.c.

² Consists of 7 ounces of milk, 2 eggs, $\frac{1}{2}$ dram of lactose, 1 square of butter, pinch of salt.

secretion will not be prevented, but the acidity in the secretion already formed will be partly or entirely neutralized.

CHART III

Date.	Hour of aspiration.	Interval after duodenal feeding was begun.	Amount of gastric secretion obtained.	Free HCl.	Total acid.	Antacid powder. ¹
<i>Patient 1:</i>						
July 18th...	10.30 A. M.	30 minutes	75 c.c.	46	56	None given.
July 18th...	4.00 P. M.	30 "	15 "	0	10	Powder given one-half hour before feeding.
July 19th...	9.45 A. M.	30 "	17 "	56	60	Powder given fifteen minutes after feeding.
<i>Patient 2:</i>						
July 21st...	3.45 P. M.	30 "	50 "	80	94	No powder given.
July 21st...	5.40 P. M.	30 "	58 "	84	100	No powder given.
July 21st...	7.40 P. M.	30 "	50 "	40	54	No powder given.
July 22d...	10.30 A. M.	30 "	10 "	0	20	Powder given fifteen minutes before feeding.
July 22d...	12.30 P. M.	30 "	18 "	0	16	Powder given right after feeding.
July 22d...	4.15 P. M.	30 "	45 "	0	18	Powder given right after feeding.
July 22d...	6.20 P. M.	30 "	54 "	4	22	Powder given right after feeding.

¹ The antacid mixture employed in these experiments consisted of from $\frac{1}{2}$ to 1 teaspoonful of the following combination: sodium bicarbonate, 15; bismuth subnitrate, 15; magnesium oxid, 10.

Thus in the treatment of gastric or duodenal ulcer by means of prolonged duodenal alimentation stress is not to be laid entirely on the exclusion of food from the stomach. Great importance is attributed to the frequent and concomitant administration of antacids or alkalies by mouth before each duodenal feeding in order to neutralize or prevent the gastric secretion which is almost regularly associated with the duodenal alimentation.

A. S. BLUMGARTEN, M. D.

In order to determine definitely the relative value of medical or surgical treatment of gastric ulcer it is essential to determine its cause. While the specific cause of gastric ulcer is unknown, there is no question that the constitution of the patient is one of the most important factors in the cause of ulcer of the stomach or duodenum. We have attempted to analyze the various phases of the constitution of the patient so as to get a more definite idea of the factors that constitute its mechanism.

In the first place, the constitution of the gastric ulcer patient and of the patient who suffers with gastric neurosis with hyper-

acidity is practically the same. We cannot differentiate them. The patient suffering with either one of these diseases has the same morphologic make-up, which seems to be more or less constant and is easily recognizable. Second, these patients also have specific physiologic factors by which they may be placed in a definite group. They all show evidence of dysfunction of the autonomic nervous system, particularly of the branches of the autonomic nervous system innervating the stomach. We have also attempted to study the inorganic chemistry of the blood of these patients. Last summer Dr. Rohdenburg and I studied the salt content of the blood in a large number of cases among whom were a number suffering from autonomic dysfunction with dominant gastric symptoms. Our studies were made on whole blood and our normal figures for calcium were from 7 to 11 mg. In nearly all of our cases of gastric neurosis or ulcer of the stomach, which we grouped together because of their same constitutional characteristics, the blood calcium figures were from 3.9 to 5.4 mg. While the number of cases was not sufficiently large to draw any definite conclusions in regard to the calcium content of the blood, they are at least suggestive. Furthermore, these patients also show objective evidence of autonomic dysfunction in the direction of vagotonia, since they give a very marked reaction to the injections of pilocarpin hypodermically. We can also recognize in many of these patients specific personality problems.

On the basis of these facts we may formulate a conception of gastric ulcer upon which methods of treatment should be based. In all probability the hyperacidity is a constitutional factor. The patients with gastric neurosis with hyperacidity, or gastric ulcer, suffer from the same type of autonomic dysfunction. The condition may be a neuralgia or an actual neuritis of some of the branches of the autonomic nervous system or of their ganglia, innervating the stomach. There may be a chemical or other underlying cause for this. These same factors probably exist in the patient with functional hyperacidity and the one who has an ulcer of the stomach. The effect of the neuritis, the neuralgia, or the radiculitis may be trophic disturbances in the mucous

membrane of the stomach, or local spasm, possibly even vesicular formation or desquamation of necrotic gastric epithelium. But what is the element that in the same type of patient produces an ulcer in one case and not in another? The ulcer may be purely accidental, simply the result of the mechanical irritation of food and gastric contents on the area of the stomach manifesting the effect of the local autonomic dysfunction. On the other hand, it may simply be the terminal effect of the same progressive process. There is no doubt that there are small ulcers which occur in gastric neurosis with hyperacidity which probably heal. Autopsy findings corroborate this. In many instances, however, the healed ulcer may leave a scar, and many of the symptoms of the gastric ulcer are due to the result of scar formation of small healed ulcers. However, in some cases the mechanical irritation or the progressive autonomic dysfunction may produce an ulcer so extensive or so deep that it cannot heal because of continued irritation.

I believe that this conception of gastric ulcer is more helpful in treatment, either medical or surgical, because it takes cognizance of the underlying factors which play a tremendous rôle in gastric ulcer. It would seem, as regards surgical therapy, that a method of surgical treatment consisting either of resection of gastric branches of the autonomic nerves or of their ganglia would offer a better prospect for cure than subtotal gastrectomy and would not be attended with its tremendously high mortality rate.

ERIC J. RYAN, M. D.

We feel that we can distinguish between a quiescent ulcer and an active ulcer, and this purely by means of the fluoroscope. Most of the gastric ulcers we get are not of the very active type. Patients complain of the usual distress immediately after eating, and that sort of thing, but they are not acutely ill. When we get an incisura the patients are really ill and they look it. Duodenal ulcer patients show marked hyperacidity of the stomach and a marked spasticity of the duodenum. The barium will not stop there, but flows into the duodenum and out again

immediately. In a chronic type of ulcer of the duodenum the duodenum remains filled for several seconds.

FRANZ J. A. TOREK, M. D.

I may say that I agree with Dr. Fischer that for gastric ulcer, especially in the lower half of the stomach, the operation which gives the best result is resection. I may say that this is true even of the perforated ulcer, of which so far this evening nothing has been said at all. In this last service of mine I have had 2 cases of perforated ulcer of the stomach in which I did a resection. The perforation in neither of the 2 cases was at the lesser curvature, which is the most frequent site. One of them was at the anterior surface, which, as Dr. Stewart has told you, is very rare, while the other was at the greater curvature. The first case was a lady sixty-four years of age who is entirely well after resection. The second case was a man also advanced in years, who was taken out of the hospital by his relatives after about three or four weeks when he developed pneumonia, and they insisted on taking him home. What became of him I do not know. This resection, I wish to repeat, is my preference only in the cases in which gastric ulcer is in the lower half of the stomach. If it is situated in the higher portions, especially near the cardia, resection would be so formidable an operation that possible gain from it would be too much overbalanced by the severity of the operation. Fortunately, it is just the ulcer near the cardia that gives us fewer urgent causes for operation, and that these patients can do better without these extensive operations we have seen. Most of them get better by a simple gastro-enterostomy, probably because the alkali which is doubtless introduced into the stomach is given with greater regularity than in any way medicinal treatment would supply it. No patient will be quite so regular in taking his medicine as the duodenum will be in putting the alkali into the stomach through a gastro-enterostomy. We have seen that there are other ways of treating the ulcer higher up in the stomach. Dr. Pribram showed us not long ago a series of cases in which the condition was improved by injecting novoprotin, and recently we have

seen a presentation in the surgical society of a case of penetrating ulcer of the lesser curvature right close to the cardia, presented by Dr. Lewisohn, of which he showed an x-ray picture, and a year later without anything being done showed a second picture in which the penetrating ulcer had become very much smaller, and in another year again presented a picture in which the ulcer had entirely disappeared. This patient had no treatment, medical or surgical, whatever, and so it is possible that these ulcers may heal without any treatment.

With regard to operation in the case of the perforating ulcer case we have to consider very strongly the ability of the patient to stand an operation. Many of them can stand nothing except a simple sewing up of the perforated ulcer, leaving additional measures to be undertaken later. Duodenal ulcers present a different problem. Here we may achieve a successful result with a simple gastro-enterostomy alone. Recently I saw a case of pyloric obstruction where the mass was about 2 inches in diameter and very firm, presenting an appearance characteristic of carcinoma to the eye and to the touch, and some glands in the neighborhood were involved. This patient, I will say, was so weak we could not offer him gastrectomy at the time, and so did a gastro-enterostomy with the intention of performing a gastrectomy two weeks later. He developed some lung complications which compelled us to postpone the performance of the gastrectomy until three weeks had elapsed, when he was taken to the operating room with the intention of removing this supposedly carcinomatous duodenal ulcer. Our surprise was great when we found no sign of it. This very large infiltrating ulcer had completely healed at the end of three weeks.

DEWITT STETTEN, M. D.

I agree with everything that the medical gentlemen have said, especially that all ulcers of the stomach or duodenum ought first to be given a thorough course of medical treatment. A certain percentage of ulcers, however, will eventually come to the surgeon in spite of the medical men, which is a fact that I think our medical friends will admit.

I shall confine my remarks to the surgical management of the cases that do come to us. First of all, I do not believe that any standardization of treatment of gastric or duodenal ulcers can be made, or that any blanket rule can be applied to all cases. Individualization in the type of surgery used is just as important, I believe, as individualization in the type of medical treatment given. The age of the patient must be considered, likewise his physical condition, and particularly the localization and character of the ulcer. Frankly, I never know exactly what type of operation I am going to do until I really see and feel the lesion after the abdomen has been opened. That is the attitude I have adopted toward gastric and duodenal ulcer. There are, of course, certain principles which can be generally applied. Active pyloric ulcers or ulcers of the lesser curvature in the lower third or half of the stomach ought always to be resected. A partial or subtotal gastrectomy should be done, followed by Billroth I or II, or by some form of the Polya technic, the procedure to be adopted depending upon the conditions found. If for no other reason pyloric ulcerations should invariably be radically resected, because it is often impossible to make a definite diagnosis of the character of the ulcer at the time of operation. Sometimes ulcers that look and feel most innocent are proved to be malignant by microscopic examination. I recall one case in which the x-ray examination showed a pyloric defect very suggestive of carcinoma. At the time of operation a pyloric ulcer was found which had a most benign appearance and feel. A resection was done and a gross examination of the specimen rather confirmed this impression that the ulcer was a thoroughly benign one. The attending physician, who, incidentally, was an experienced pathologist, agreed that the specimen, after it was out of the abdomen, and was thoroughly palpated and inspected, did not suggest malignancy, and yet microscopic examination showed the ulcer to be carcinomatous. Further, the resection of a pyloric or lesser curvature ulcer is a relatively simple operation, because the stomach is usually dilated and mobile and there is generally sufficient gastric stump left for a proper anastomosis of the stomach and intestine. The risk of resection in this type of

case is probably not much greater than an ordinary gastro-enterostomy. As a rule the postoperative course is astonishingly simple and the final result a permanent, radical cure. Ulcers very high on the lesser curvature, or extensive saddle ulcers, even lower down on the lesser curvature, are not always suitable for subtotal gastrectomy. Theoretically the operation might be indicated, but because of technical difficulties and the greater risk to the patient it may not be practicable. Even in the hands of expert surgeons, very familiar with gastric surgery, the mortality in these cases is very high and a more palliative procedure should be attempted. Excision or cauterization of the ulcer combined with gastro-enterostomy often gives good results. In healed ulcers of the pylorus with cicatricial stenosis posterior retrocolic gastro-enterostomy probably gives the most satisfactory results in gastric surgery. I know of no other operation on the stomach, not excluding subtotal gastrectomy, in which the immediate postoperative recovery is usually so easy, in which the end-results are so uniformly satisfactory and gratifying, and in which the patient is so permanently and thoroughly cured as by this operation performed for this disease. It may be that in these cases with healed, cicatrized ulcers the ulcer tendency has been overcome and that the danger of subsequent ulceration either in the stomach or pylorus or at the gastro-enterostomy stoma no longer exists. In perforated ulcers of the stomach or pylorus, as a rule, simple suture of the ulcer is performed with an added gastro-enterostomy, providing the perforation is no older than twelve hours, and if the condition of the patient is favorable. This is especially advisable if the suture of the perforation produces a stenosis of the pyloric opening. It has been suggested that even in perforated ulcers, provided the perforation is sufficiently recent, say no older than twelve hours, that a primary resection should be done. This procedure has been practised with success by some of the European surgeons. Up to the present I have felt, however, that in the face of the infection that is necessarily present with a perforation, such an extensive operative pro-

cedure is contraindicated, although one might succeed with this in certain favorable cases.

As regards duodenal ulceration the situation is not quite so clearly defined. First of all, I do not believe that the acid factor in ulceration has been definitely proved. The duodenal contents are naturally alkaline even in the presence of considerable gastric hyperacidity, and the assumption that subtotal gastrectomy, by removing the acid factor of the stomach in the prepyloric region and rendering the stomach anacid, prevents duodenal, jejunal, or gastrojejunal ulceration, has, to my mind, never been definitely demonstrated. There is also some question as to whether or not the production of total gastric anacidity is a desirable goal. There further seems to be a great difference of opinion in the percentage of marginal or jejunal ulcers following gastro-enterostomy. At Mount Sinai Hospital it is claimed that their percentage runs as high as 34 per cent. Fortunately that has not been our experience, nor has it been the experience of many other surgeons who have practised gastro-enterostomy and who have carefully followed up their cases. The general impression is that 5 per cent. of gastrojejunal or jejunal ulcers would be a high figure. It may be that the racial factor in the patients has some influence on the statistics from the Mount Sinai Hospital. In general, our attitude toward duodenal ulcers is that if the ulcer is a chronic infiltrated one penetrating into the pancreas or toward the liver, a resection with a subtotal gastrectomy is advisable provided the technical difficulties of the operation are not too great and that the patient's life is not placed in jeopardy by the operative procedure. In cases of infiltrated, penetrating duodenal ulcers, where the technical difficulties are so great or the patient's condition is so poor that primary resection would jeopardize the patient's life, I believe that, should resection be deemed indicated, the operation should be performed in two stages. A primary gastro-enterostomy should be done, followed by a partial or subtotal gastrectomy after the patient's condition has improved and some of the inflammatory reaction around the ulcer has subsided. This principle can also be applied to pyloric or lesser curvature

ulcer under similar conditions. In small, superficial, more acute ulcers, or cicatrices indicative of healed ulcerations, which may or may not produce duodenal stenosis, I still prefer a simple posterior retrocolic gastro-enterostomy as a relatively minor and safer procedure. I may possibly at some later date change my opinion on this point, but at the present time the seriousness of the operation of subtotal gastrectomy, in this type of case, seems to me to be out of all proportion to the severity of the disease. In perforated duodenal ulcers the ulcer is closed by suture, and, if the perforation is no older than twelve hours and the patient's condition is favorable, an added gastro-enterostomy is performed, especially if a narrowing is produced by the suture closing the perforation.

CARL EGGERS, M. D.

During a recent symposium on the treatment of gastric and duodenal ulcer at the Academy of Medicine the speaker, who is an advocate of subtotal gastrectomy as the proper treatment for all ulcers, whether gastric or duodenal, said among other things: "When I formerly entered a medical ward of our hospital I felt ashamed, for all around me were patients on whom I had done a gastro-enterostomy, and they had not been cured thereby. But since I have done resections none of my patients come back to the medical wards for treatment." With such an experience he was no doubt justified in his enthusiasm for resection as the method of choice. In our hospital, I feel quite sure, the surgeons do not have to be ashamed to enter the medical wards, for somehow their experience does not coincide with that of the surgeon mentioned. We are all agreed, the medical men and the surgeons, that some patients with ulcer had best be operated on. As to the exact procedure we are influenced by our own experience.

My belief at the present time is that one should not generalize too much, but rather treat each case as seems best. The first thing to be sure of is whether there is really an ulcer present. Gastro-enterostomy is an operation devised to overcome pyloric obstruction of greater or less degree, produced either by spasm,

the result of an ulcer, or by actual scar contraction. When applied to this group of cases I believe the results are excellent. On the other hand, if done for a simple spasm of the pylorus in a neurotic individual with hyperacidity I believe the results are going to be far from satisfactory.

No operation on the stomach should be undertaken on a snap diagnosis of ulcer. One should be sure of one's findings as nearly as possible, and the patient should have had the benefit of medical treatment. If that has failed, or symptoms return after temporary improvement, one may operate. Even then an ulcer is not always found. One may feel a pyloric ring which impresses as somewhat thickened, but that is not enough to do a gastro-enterostomy. Such a thickening may be only a spasm. I watch such a spasm for awhile, feel it repeatedly, and in the meantime look for other conditions which reflexly may be responsible for the stomach symptoms. The patient may have an old adherent appendix, or a diseased gall-bladder, or, if a female, there may be pelvic disease which could not be diagnosed in advance. At any rate, such conditions should be attended to, and if one later returns to the stomach the impression may be that no lesion exists there. I have sometimes found that in patients in whom even the x-ray pointed to an ulcer, one should not be driven into doing a gastro-enterostomy, and one should not feel ashamed to admit that no ulcer is present, and do a gastro-enterostomy simply to justify the operation.

But if an ulcer is really found, what should be done?

In duodenal ulcer my practice has been to do a posterior short loop gastro-enterostomy, both for the simple and penetrating ulcers, and from my own experience I propose to continue that practice. It seems to me unsurgical to remove one half a stomach for a little duodenal ulcer. The reason given for sacrificing such a large part of the stomach is that the acid-producing area has to be removed because that is apparently responsible for the production of gastrojejunal ulcer. If that is so, I would say one should rather find a way to reduce the acidity by medical means. And it has not been proved that ulcer formation, either originally or secondarily at the margin

of the stoma, is due to hyperacidity. Other factors have to be considered, and I believe the most important is a proper suture line, which approximates the mucosa in such a way as to prevent gastric juice from getting on to the cut surfaces and in between the layers of the walls of the viscera. That gastro-enterostomy, if properly performed, and with the right indication, gives excellent results, there is no doubt. Ulcers heal and the pylorus again becomes patent.

I have reserved resection in duodenal ulcer for those cases in which there was special reason for doing it. Either for cases which had had repeated hemorrhages or for those which looked malignant. There is no doubt that it gives excellent results.

For gastric ulcer, on the other hand, I have used radical procedures in preference, and the more conservative gastro-enterostomy in only certain patients with multiple ulcers, with acute perforation, or those whose general condition contraindicated subtotal gastrectomy. The results of resection have been uniformly good. I usually use the Billroth II method, and occasionally the Polya-Balfour.

As I said before, though, it is not only a question of what is done, but how it is done. There is no doubt that some patients have postoperative disturbances, and many of these may be traced to poor technic or an error in technic. This has been well illustrated to me by a number of patients on whom I have had to do secondary operations. The majority had most extensive adhesions between the stomach, liver, and abdominal wall. One had a hernia behind the gastro-enterostomy, another had a loop placed in the wrong direction, with angulation of the gut, etc. Certain it is that all patients with postoperative disturbances following gastro-enterostomy do not have a jejunal ulcer. In my experience, meaning by that not only my own cases but those of others whom I have observed, this is very rare. I can recall having actually seen only 2 cases. I may mention in passing that I have at present 2 patients in my own practice who give symptoms suggestive of a marginal or a recurrent ulcer. On one of these I performed a gastro-enterostomy for duodenal ulcer in 1912, now fourteen years ago, and

on the other a subtotal gastrectomy for multiple ulcers and pyloric obstruction in 1917, now nine years ago. Perhaps when we have observed gastrectomy cases longer we shall find that there are some among them who are not doing as well as had been expected.

G. BUCKY, M. D.

I have had the pleasure of attending quite a number of symposiums on gastric ulcers. We hear often of medical treatment and surgical treatment, but we do not hear anything about the physical treatment of these cases. This may be explained by the fact that the physical means of treatment are not developed up to date to the extent that we can speak of the fundamentals of physical treatment. I do not believe there can be any question that ulcers have to be considered as a disease of the nervous system generally speaking. This takes into consideration the constitutional factor also. Why don't we treat the nervous system in such cases? Why don't we treat the autonomic nervous system? I think we would come closer to the solution of this question if we would take into consideration the work of E. F. Mueller, who has shown that there is a close connection between the skin and splanchnic organs. They are, in regard to the autonomic system, in a certain stage of balance. Every disturbance which we produce in the sympathetic parasympathetic balance of the skin is answered at the same time by a balance disturbance of the splanchnic organs in just the opposite direction. Without going further into the details of this very interesting problem I wish only to mention that E. F. Mueller and Peterson (Chicago) proved this opinion by careful studies of the distribution of the leukocytes and changes in the permeability of the vessels in the periphery and the splanchnic organs. E. F. Mueller has also shown that intradermal injection of any substance produces such a disturbance in the autonomic system.

Now, I have been working for four years on a new x-ray method which I shall present at the next meeting of the German Medical Society. To use a certain kind of x-rays which are

entirely absorbed in the skin, and which I myself and E. F. Mueller have proved, have also a marked effect on the parasympathetic endings in the skin. I tried, therefore, to use these rays for the purpose of influencing splanchnic organs through the skin and I started with treating ulcer cases.

I wish to mention only that I now use a treatment like this, giving these treatments over a large region of the skin in cases of ulcer of the stomach and duodenum, and that astonishingly enough in the course of three or four weeks these cases have become well, even where they had been suffering from twelve to fourteen years with ulceration. They have gained in three to four weeks 5, 6, and 7 pounds in weight and have been able to eat everything. I think if we consider that we can treat the autonomic nervous system much better physically than with other means, we ought to try it, and I believe Dr. Laporte has already met with a similar experience, especially with diathermia, which has given similar results.

JOHN C. A. GERSTER, M. D.

On the service of Dr. A. A. Berg, at Mt. Sinai Hospital, we have seen a large number of ulcer recurrences either at the original site or at the margin of the gastro-enterostomy. Whether the use of clamps and the serial ligation of vessels as encountered in the submucosa is a predisposing factor in the production of ulcer remains a question. I know that Dr. Beer has considerable gastric material at Bellevue, but rarely uses clamps, doing most anastomoses with the aid of traction sutures. He does not see anything like the number of recurrences observed at Mt. Sinai.

Of course, there may be racial disposition to ulcer formation, as has been suggested by Dr. Meyer.

In the return clinic one can practically distinguish by their facial expression the resection patient cases from the gastro-enterostomy patients. The resection patients give their answers promptly and cheerfully, and seem to be restored to normal health, whereas the gastro-enterostomy patients admit they are better, but recite a long list of complaints.

I wanted to ask Dr. Eggers whether his case of stomach resection with possible marginal ulcer showed any free acid in the Ewald test-meal. It has been claimed that in resection cases whose postoperative test-meal showed no free acid one never observed recurrence of ulcer. In 1 or 2 cases where an insufficient amount of stomach had been removed and hyperacidity persisted, a marginal ulcer had formed within a year after operation, and that upon further removal of the remainder of the acid-bearing part of the stomach there was no more trouble.

The disappearance of hard, indurated masses involving the stomach wall, simulating carcinoma, similar to the case cited by Dr. Fischer, have also been observed by me. In one, a large ulcer apparently a carcinoma, was close to the cardia, and posterior gastro-enterostomy was done. The man has been well four years. Why some of these ulcers get well and why others persist is still an unexplained fact.

WILLY MEYER, M. D.

The goal of the physician's and surgeon's treatment of gastric and duodenal ulcer is to put the patient into such a condition that he has no more pain, that he can partake of any kind of food, and that he can work. Naturally, he may remain under his physician's observation and care, but it is to be demanded that he is able to carry on the ordinary average day's work without suffering. This point of view refers to the laborer and the individual who with his family is dependent upon his daily work. The well-to-do can look at the question from a different standpoint if he prefers.

If I were an internist or specialist and would see such a patient early, I think that I would first make sure that the diagnosis had been correctly established. Then I would order the patient to bed, for rest of the general system, and also impress upon him the necessity of putting the stomach itself at rest; in other words, put him on duodenal feeding. I would further add intravenous injections of "novoprotin" on the basis of Pribram's recommendation. The latter was here three years ago and made,

I am sure, the impression on every one of us of an absolutely conscientious observer. As one of the staff of Professor Bier's Surgical Clinic at Berlin he has published later a series of more than 300 cases in whom at first only "novoprotin" was used in the treatment of gastric and also a few duodenal ulcers. If such a man tells us that in 50 to 70 per cent. of these more than 300 cases the former severe pain disappeared, that the patient could take ordinary diet after awhile without distress and return to his work, the method certainly is worthy of consideration.

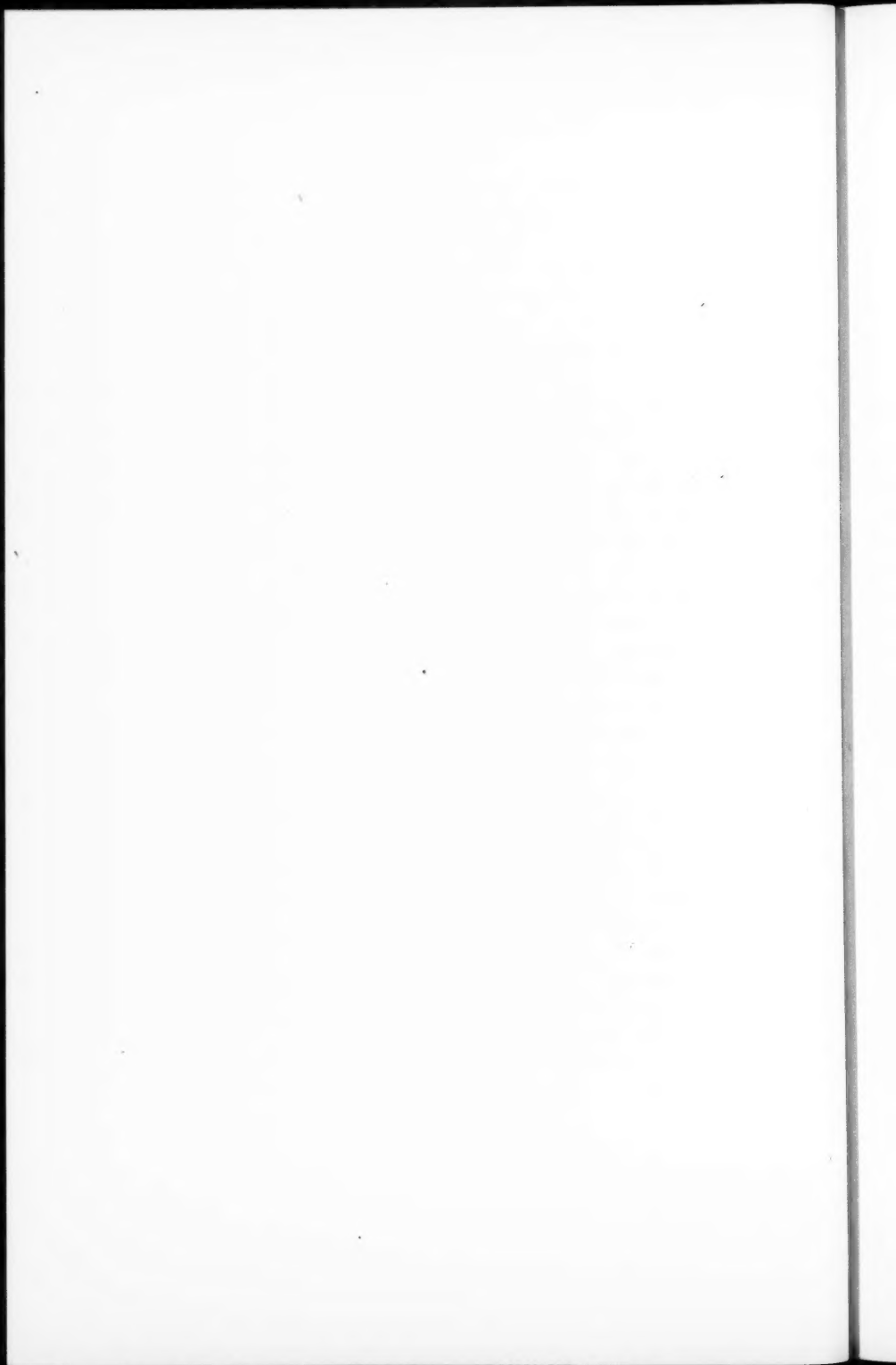
After three weeks in bed I would let the patient get up, and then, according to results, eventually repeat the novoprotin injections after four or six weeks, and, if indicated, once more with the same interval. If then the patient was not improved and was unable to work I would say: here now is the indication for surgery.

According to the discussion presented here this evening, it seems that our attending surgeons are all in accord with regard to the treatment of gastric ulcer. When we have the stomach right before us and can divide it within healthy tissue they agree that resection is best. I join their ranks. Some of these cases certainly become carcinomatous in course of time. Whether this happens in the greater percentage of cases is still under discussion. Still I believe with the majority of my colleagues that it is wise to resect these stomachs either by the method of Billroth I or II, or a modification of either.

As for the duodenal ulcer let us remember that those American surgeons, who urge wide gastric resection in these cases at present, have done so on the basis of their finding so many gastro-jejunal ulcers after gastro-enterostomy: in 30 to 35 per cent. of their cases. We at the Lenox Hill Hospital have not seen this. I must say that in all of my life I have not seen more than 2 patients who developed a marginal ulcer after I had performed gastro-enterostomy upon them, and I have done a great many gastro-enterostomies. Some of these patients may have gone elsewhere later on and I have not seen them. But still I think I would have heard of many of such late complications at my hands. How can such discrepancy be explained? Not con-

sidering technical points during operation, may it not be that the human material operated upon as such has something to do with the high percentage of marginal ulcers seen: "One-third of all patients subjected to gastro-enterostomy"? I feel that the condition of the sympathetic nervous system of many immigrant Hebrews cannot bear all that is put upon it. And the sympathetic nervous system seems to play an important rôle in the etiology of gastric ulcer as well as of duodenal ulcer. Personally I am not—or shall I say I am not yet—in favor of wide gastric resection in the presence of duodenal ulceration. I do gastro-enterostomy in these cases, and cannot agree with those who favor the radical method, that the regular entrance of bile into the stomach subsequently to the formation of the anastomosis has nothing whatever to do with the beneficial effect of the operation. I rather believe that the presence of bile in the stomach contents neutralizes the acidity to a great extent and plays a decided rôle in the healing of duodenal ulcer.

Summing up, let us emphasize that the annals of this chapter of borderline disease are not yet closed. We have yet to learn a great deal about it and must try to decide what is best for the individual patient.



CLINIC OF DR. I. W. HELD

BETH ISRAEL HOSPITAL

ANEMIA. A CLINICAL AND HEMATOLOGIC STUDY

LITERALLY speaking, anemia signifies lack of blood or impoverishment of blood. Anemia is a symptom and not a disease. It is brought about by the destruction of red blood-cells when either the blood formation cannot keep pace with the blood destruction, or regeneration is primarily below par, or, what is most common, a combination of both. The diagnosis of anemia must not be made on the basis of pallor of the face, mucous membrane of the lips, and palpebral conjunctivæ. It cannot be emphasized too strongly that pallor even of the mucous membrane may be present without any changes in the hemoglobin or red blood-cells, as, for instance, in psychopaths or neuropaths, some cases of arteriosclerosis, in chronic lead-poisoning due to contracted peripheral arterioles, also in chronic nephritis with edema, in tuberculous adenopathy, in incipient apical tuberculosis, and often in individuals whose skin is devoid of natural pigments. On the other hand, dilated peripheral blood-vessels may give a reddish tinge to the skin even to the anemic patient, or the pallor may be masked by an existing icteric tinge (hemolytic icterus), actual jaundice, or by pigmentation of the skin (Addison's disease). The deficiency in the hemoglobin may in some cases be compensated either by an increased blood flow or by the venous blood less saturated with oxygen than normal. This process is a compensatory phenomenon and explains the absence of some marked subjective symptoms in severe anemia. The diagnosis of anemia, therefore, must not be made without a hematologic study.

The history of hematology begins with Virchow, who first

described leukemia, Neumann who discovered nucleated red blood-cells in the bone-marrow, and the classical work of Ehrlich, who discovered the finer methods of staining which enable us to differentiate the various forms of blood-cells. Of the two main constituents of the blood, the cells and the serum, hematology deals with the subject of the cells, their origin, development, morphology, and function. Clinical hematology deals with the behavior of the blood-cells in disease, changes in the cells, particularly the cytomorphologic composition of the blood, as well as the pathogenesis and diagnostic value of these pathologic changes.

Anemia may be due to: (a) Affections of the erythropoietic apparatus; (b) leukoblastic apparatus; (c) disturbance in megacariocytes; (d) lymph-glands; (e) combination of all these factors. It is a clinical fact that primary affections of either the leukoblastic apparatus, lymph-glands, or megacariocytes produce definite changes in the erythropoietic system; whereas a primary affection of the erythropoietic system need not cause changes in other parts of the hematopoietic apparatus, or only in very rare instances. This explains why marked changes in red blood-cells are present in leukemia, thrombocytopenia, diseases of the lymph-glands (splenic anemia or pseudoleukemia). In most cases of primary and secondary anemia where the erythropoietic system is involved, the changes in the leukocytes are very insignificant, and the activity of the megacaryocytes may be impaired only quantitatively as indicated by a decrease in thrombocytes in the majority of cases of anemia, except in chlorosis, where there is an increase in thrombocytes. Qualitatively, however, the thrombocytes are not impaired in such diseases where the erythropoietic system is primarily involved, which explains the reason why in many cases of secondary and even primary anemia there is no hemorrhagic diathesis.

It has been customary to term all affections characterized by pathological changes in the blood-cells as blood disease. This is incorrect. In reality, the changes that take place in the cellular element of the blood are not, as a rule, caused by disease of these cells, but by an affection of the hematopoietic system. It would

be just as incorrect to call a disease a blood disease because of the pathologic changes in its chemical constituents (hyperglycemia or increased non-coagulable nitrogen). There are but few diseases of the blood which primarily affect the cellular element proper and may, therefore, be rightfully termed blood disease, as, for instance, the blood changes caused by malarial parasites or by hemolytic and chemical poisons. In the majority of instances where pathologic changes in the blood occur the primary seat is in the hematopoietic organs. The reason that we have to resort to the term "blood disease" is because of our inability to study the blood directly in the hematopoietic system, as rightfully pointed out by Drinker. The changes in the hematopoietic system, therefore, can only be determined through the blood-picture.

ANEMIA ASSOCIATED WITH AFFECTIONS IN THE ERYTHROPOIETIC APPARATUS

Before discussing anemia a brief review of the embryology of the blood-cells is in order.

Formation of Red Cells.—Early in fetal life the red blood-cells originate from the walls of the primitive blood-vessels, later in the liver and the spleen. The liver loses its blood forming quality very early, whereas the spleen and lymph-glands retain the formation of lymphocytes, the former retaining that property during extra-uterine life. Toward the end of fetal life and throughout extra-uterine life the formation of red blood-cells takes place in the bone-marrow. Up to the age of sixteen this process goes on in the bone-marrow of all the bones, and after sixteen it is confined to the spongy flat bones, and in part also to the heads of the long bones, especially the femur and humerus. Up to sixteen, therefore, the bone-marrow of the long bones is red, and after sixteen the bone-marrow becomes yellow because the production of red blood-cells has ceased there.

Under pathologic conditions the blood-making organs resume their embryonic property, and the first organ to do this most effectively is the bone-marrow, which in case of overproduction of red cells turns completely red. If the overproduction affects

the white cells, the bone-marrow is grayish red, and if there is complete exhaustion, the bone-marrow becomes yellowish white and watery, as is the case in aplastic anemia and in malignant cachexia. Under very rare conditions even the liver may resume its blood-forming property, as first pointed out by Meyer and Heinicke,⁶⁰ Draper,¹⁹ and Schridde.⁸⁴ These authors found islands of embryonic blood-cells in the liver in severe forms of anemia.

As evidence of a pathologic state of blood formation, changes in the cellular elements of blood take place which indicate variations in bone-marrow function. The blood-picture changes its character, indicating that the hematopoietic organs (bone-marrow, spleen, and lymph-glands) have resumed their embryonic function.

In the blood of the human embryo large nucleated red blood-cells are present which are known as megaloblasts. In the very early embryonic stage the nucleus occupies the greatest part of the cell. Its structure is fine, soft, and net-like, and stains weakly with basic and oxychromic dyes. The protoplasm of the megaloblast is at first basophilic, later strongly basophilic and polychromatic. Eventually the basophilic intensity increases, the nucleus becomes smaller and dense (piknotic), and the fine network disappears. At times the nucleus when disappearing subdivides into three or six nuclei. At that stage the protoplasm of the cell has already developed its full affinity for acid dyes as a sign of full ripening. This tendency to normal staining is known as orthochromasia. The megaloblasts have now been converted into embryonic megalocytes which are very rich in hemoglobin. Before the megaloblasts have entirely disappeared another unripe stage is encountered later in embryonic life, in the form of normoblasts. These are considerably smaller than megaloblasts, being 8 to 12 microns.

There is another form of nucleated embryonic red cell which contains hemoglobin, termed by Naegeli⁷⁰ "macroblast," and by Ferrata "pronormoblast," which is also known as "hemoblast." Drinker²¹ adheres to the term "hemoblast." This is the youngest form. Its cell body is irregular in form and stains a darker blue

with methylene-azure-eosin stains than the nucleus. Drinker's method of staining is the best. One drop of 1:300 aqueous solution of cresyl blue is placed upon a slide and a drop of fresh blood is placed on the stain and a cover-slip quickly adjusted and rimmed with vaselin. It contains no hemoglobin. Because of this staining quality it resembles the lymphocytes, so that Pappenheim⁷⁴ considered it a "prolymphocyte." Sometimes such cells are encountered in the circulating blood in severe anemia during childhood. There are also microblasts which are somewhat smaller than normoblasts, but have no other distinctive characteristics. The ripening process in the denucleation of the normoblast is exactly the same as that of the megaloblast. By the process of kariolysis the red cells increase and the nuclei disappear, so that in postuterine life no nucleated red blood-cells reach the circulation under normal conditions. The normoblast is the mother-cell of the normocyte.

The normocyte is a biconcave or cup-shaped disk which is sometimes biscuit shaped. It contains no nucleus and is yellowish in color when unstained; measures about 7.5 microns and takes on an orange color with acid stains. The surface is not stained uniformly. There are bright zones in the cell indicating that the hemoglobin is not equally distributed. The erythrocyte is exceedingly elastic. The most important part of the erythrocyte is the hemoglobin, the function of which is to transfer oxygen to carbon dioxide from the tissues. Within the cell there are also salts, cholesterol and lecithin, which appear to exert an important function in retaining the hemoglobin within the cell membrane. The outer limiting membrane is a homogeneous structure, colloidal in character, and permits free passage of osmotic currents. The red cell maintains its shape in the serum or in physiologic salts (0.85 per cent. solution), but when placed in concentrated salt solution the cell shrinks, or if the salt content is decreased, the cell swells, and finally ruptures, allowing the hemoglobin to escape. This property of red cell to break in hypotonic and hypertonic salt solution is important from the pathologic standpoint and will be discussed in connection with hemolytic icterus. The normal red cell has uniform staining

quality known as orthochromasia. Disturbance in hemoglobin content of the cell changes the staining quality, either taking on very little stain (hypochromasia) or excess of stain (hyperchromasia) or both acid and basic stains (polychromasia). Another important element in the study of red cells because of its significance in disease of the blood-making organs is the reticulated red cell. Benda⁸ described these cells under the term "miochondria" to indicate certain granulations in the cytoplasm of cells concerned in spermatogenesis. They are found in all the cells in the human body. They are an essential accompaniment of nuclear conditions and are of importance to us in red cells, since they disappear as the cells reach the age at which they normally function. Because these elements are freely strung together in skein-like arrangements they have been properly designated as reticulated red cells. In the normal blood they are encountered in about 0.5 to 1.5 per cent. Under pathologic blood conditions they may be present in 20 to 30 per cent. or even 40 per cent.

The red blood-cells are not subject to any marked quantitative or qualitative changes under physiologic conditions. There are usually about 5,000,000 red blood-cells in man and about 4,500,000 in woman. In normal individuals formation and destruction of the red blood-cells harmonize in order to maintain the constant concentration of the blood-stream. The main function of the red blood-cell is to carry oxygen and to a lesser degree carbon dioxid—a functional compensation by the hemoglobin. Altitudes and barometric pressure influence changes the number of red blood-cells. As we pass from a low to a high altitude we experience a lowering of the oxygen pressure.

In order to achieve an adequate oxygen supply for the tissues under such conditions, and have the circulatory rate constant despite the greater need for oxygen, the number of corpuscles and the amount of blood is increased. It is possible that in passing through a high altitude both factors—increase in red cells and development of a power to pass oxygen into the blood-stream on the part of the cells of the pulmonary alveoli—are involved. That there is an increase in the cells and

hemoglobin is absolutely certain. Haldane³³ proved that the pulmonary epithelium shows active adaptation at high altitudes.

Another rare condition in which a temporary physiologic increase of the red cells takes place is acute polycythemia produced by injection of adrenalin, as first demonstrated by Lanson.⁴⁸ He attributed this increase to a constriction of the capillaries caused by the adrenalin. Mental excitement, hyperactivity of the suprarenals, excessive exercise, very hot baths also produce temporary increase in red blood-cells, not the result of overproduction of bone-marrow, but probably dislodgment of red cells from the liver into the peripheral circulation. Passing from a low to a very high altitude causes polycythemia. Sudden but not fatal obstruction in the portal circulation often causes increase in red blood-cells. They are also considerably increased in the newborn. Qualitative changes in the red blood-cells under normal conditions are, as a rule, not encountered.

Blood-platelets.—Another important normal element of the blood which must be mentioned is the megacaryocyte and its derivative, the blood-platelet. Wherever red blood-forming tissue is found the megacaryocyte is also encountered. The nucleus of this cell is ring shaped and seems to be made up of large vesicular nuclei. The nucleus is very seldom lobulated. The megacaryocyte arises, according to Brebichin,⁹ from the osteoblast. Blood-platelets are encountered late in embryonic life. This view is supported by Howell.³⁷ The stronger the erythropoiesis, the more numerous are these cells. This would prove that the view of Wright and his co-workers, Kiebel and Mall,¹⁰⁴ that the megacaryocyte is derived from the smaller mononuclear elements, is not correct. The view of Wright,¹⁰³ however, that the megacaryocyte is the mother cell of the blood-platelet, is the correct one. The megacaryocytes are found most numerous surrounding the capillaries. They have ameboid movements, and by such movements their cytoplasm find their way into the blood-vessels and eventually break up into clumps of blood-platelets which circulate freely and have ameboid movement. The blood-platelets are the principal source of blood thrombin and an indispensable factor in blood coagula-

tion. They also furnish a certain amount of thromboplastin or thrombokinase, another factor in the process of coagulation. In the process of erythropoiesis and that of red blood-cell destruction the blood-platelets play an important rôle. Normally, they number about 350,000 to the cubic centimeter and are somewhat smaller than the erythrocyte, sometimes they are larger. They may show grouping of granular material into conventional nuclear shape. Their clinical significance will again be discussed in connection with thrombocytopenia. It is interesting to mention here that Minot and Lee showed that the blood-platelets in hemophilia while in no way differing in appearance or number, differ qualitatively in their unreadiness to break down and give up the blood thrombin which originates in them.

Leukocytes.—The leukocytes in the circulating blood of the embryo, as well as in the human fetus, appear considerably larger than the nucleated red cells, and are for a long time present in very small numbers. Those that appear first are typical myeloblasts with equally distributed protoplasm and nucleus, as seen in the cells of the bone-marrow and in the peripheral blood and postembryonically in cases of leukemia. The myeloblasts are followed by myelocytes of neutrophilic and eosinophilic nature as well as monocytes, and eventually by lymphocytes. All investigators agree that lymphocytes appear very late in embryonic life. In post embryonic life the number of white cells vary from 6,000,000 to 10,000; of these, about 72 per cent. are polymorphonuclears, 2 per cent. eosinophils, 20 per cent. small lymphocytes, 5 per cent. large lymphocytes, and 1 per cent. transitionals. The most important function of leukocytes is phagocytosis, a property intimately associated with their ameboid movement. Muir⁶⁷ found that the ameboid movement begins to appear as the nucleus becomes polymorphous. Carnege¹⁴ observed ameboid movement and phagocytes in the myelocytes. This is confirmed by Drinker. The phagocytic power depends to a marked degree upon alteration in surface viscosity. The polymorphonuclear neutrophils do not only take up most bacteria, but they digest them very readily. This digestion is accomplished through the medium of proteolytic

ferments. In addition, protease, lipase, amylase, maltase, and oxidase have been identified as endo-enzymes of these cells.

Physiologic leukocytosis occurs under a great number of conditions. It is known that the number of leukocytes vary in the course of the day. Ellermann and Erlandsen, quoted by Naegeli, found the following changes in the normal individual in the course of the day: At 6 A. M. 7400, at 10 A. M. 8800, at 3 P. M. 9200, and at 7 P. M. 10,000. They believe that the change is due to the increased cardiac activity in the course of the day, and the greater the muscular activity, the more marked the leukocytosis. This would explain leukocytosis after active exercise and cold bathing. Leukocytosis after a meal at the height of digestion is a very frequent occurrence, and according to some authors it is more marked after the intake of protein food than after carbohydrates. Some authors claim that carbohydrates cause an increase in lymphocytes, whereas fatty food increases the neutrophil cells. Leukocytosis occurs very frequently during pregnancy, particularly during the latter part. This is, however, not present in all cases, and, unlike the older authors, who used to attribute diagnostic and prognostic importance to the leukocytosis during pregnancy, it is today well known that many normal pregnancies may show no leukocytosis. On the other hand, pathologic pregnancies may and may not give rise to leukocytosis. During delivery and the beginning of puerperium a leukocyte count of 20,000 may be encountered. The newborn has also for the first few days considerable leukocytosis. The physiologic increase of granulocytes is mostly that of neutrophils. There has been a great deal of discussion as to the significance of physiologic changes in the number of leukocytes. Most interesting and enlightening are the studies of Mueller and Peterson⁶⁷ at the University of Illinois.

Mueller found the normal changes that take place in the number of leukocytes in the peripheral blood are due to a disturbance in the vegetative nervous system controlling the innervation of the blood-vessels. He found that a sudden diminution in the number of leukocytes in the peripheral blood can be produced experimentally by causing parasympathicus

reaction in the splanchnic vessels and sympathetic reaction in the blood-vessels of the skin. He showed that the ripe neutrophilic leukocytes gather in that part of the vascular system where the parasympathicus influence predominates causing dilatation of the corresponding vessels. An increase in polymorphonuclear leukocytes is brought about by parasympathicus impulse, and diminution in such cells is the result of predominance of sympathetic influence on the blood-vessels. The first experimental proof of this was made possible when Mueller⁶⁶ showed that a high peripheral leukocytosis can be caused by insulin shock. This phenomenon, which was observed in man, was experimentally demonstrated in dogs. After insulin the dogs do not get symptoms of shock, but the leukocytes go up as high as 40,000, and this can be reduced if 20 c.c. of a 20 per cent. solution of peptone is injected into the blood. The animal which shows the insulin hyperleukocytosis in the peripheral blood also shows a marked diminution in the leukocytes in the blood obtained from the liver region. Those animals which show after injection of peptone hypoleukocytosis in the peripheral blood have a hyperleukocytosis in the blood in the liver region. The studies of Peterson⁷⁶ determined that in cases of peripheral leukopenia after the administration of peptone there is an increase in the endothelial permeability in the splanchnic region which disappears when peripheral leukocytosis takes place. In other words, insulin shock by causing leukocytosis, brings about a decrease in the endothelial permeability in the splanchnic region; whereas, peptone, which causes a leukopenia, causes, in turn, an increase in the endothelial permeability in the splanchnic region. Increase in permeability indicates vasodilator influences; decrease in permeability speaks for vasoconstriction.

We note further that the parasympathicus influence is that of vasodilatation, whereas the sympathetic causes vasoconstriction. Experimental leukopenia, therefore, is accomplished by parasympathicus influence in the splanchnic region; whereas experimental leukocytosis is accomplished by sympathetic influences in the splanchnic region. From this the conclusion may be drawn that wherever the parasympathicus influence pre-

dominates in a vascular region an accumulation of ripe neutrophilic leukocytosis takes place. Acute leukopenia, on the other hand, indicates the influences of sympathetic predominance.

Mueller and Peterson showed experimentally that peripheral blood-vessels and those in the splanchnic region are under the same nervous influences, and they term this influence "splanchno-peripheral autonomy." By this is understood that both these organ groups (periphery and splanchnic regions) are so constituted that under normal conditions they never react alike to innervation influences. If, for instance, on account of some definite cutaneous irritation, a narrowing of the skin vessels takes place, those in the splanchnic region dilate irrespective of what the cause may be. The well-known physiologic variations of the number of leukocytes are an indication of the accommodation of leukocytes to fine changes in this splanchnic peripheral autonomy.

The splendid work of the above named authors explains most satisfactorily the physiologic changes in the number of leukocytes in most conditions, as, for instance, after active exercise, after hemorrhage, febrile disease after the administration of certain drugs, such as collargol, camphor, salvarsan, benzol bodies, etc.

It is very interesting to note that Wells⁹⁸ found a marked decrease of the polymorphonuclear leukocytes in the peripheral blood of rabbits a few minutes after the intravenous injection of dead bacteria. At the same time the blood from the splenic and hepatic parenchyma shows an enormous increase in leukocytes. The blood obtained from the lung parenchyma does not show such an increase. If living bacteria were injected directly into the liver and spleen leukocytosis was caused in these organs. Winternitz¹⁹² showed that simple irritants cause mild local reaction with a moderate leukocytosis. Active irritants which produce sterile pus cause high local leukocytosis.

Ewing, in his excellent book on Clinical Pathology of the Blood, states that the breaking down of the bone-marrow as a result of infection or metabolic disturbance may bring into the blood a large quantity of normal and abnormal white cells; agonal

leukocytosis is thus explained. There may also be a gradual white cell aplasia in the bone-marrow causing almost a disappearance of the white cells from the circulating blood. Longcope⁵⁴ noted at autopsy a depletion of the bone-marrow taken in regard to polymorphonuclear leukocytes as compared with rib marrow resected during life. He investigated the changes in the bone-marrow at the terminal stages of acute infections. In many such instances the leukocytes in the blood diminished steadily until death occurs and may disappear almost completely from the bone-marrow. The different types of white cells are also subject to quantitative changes under a great number of conditions, as exemplified by eosinophilia in parasitic disease, vagotonia, asthma, and colicomucosa; lymphocytosis in tuberculosis, syphilis, status thymicolymphaticus, Basedow's disease, by polynucleosis in suppurative disease, and by monocytosis in splenic anemia. In most infectious diseases the eosinophils are increased for a short time after the infection has subsided. The white cells are often subject to transient qualitative changes, as first pointed out by Arneth and later by Schilling, which, according to these authors, also have a great diagnostic and prognostic importance. The lobules in polymorphonuclear leukocytes, according to these authors, may be considerably reduced in number, depending upon the severity of the infection; therefore in severe cases the nucleus may consist of one large lobule approaching in resemblance the myelocyte, which indicates the appearance of the unripe white cell in the circulating blood.

MORPHOLOGY OF ANEMIA

Before discussing the symptoms of anemia it may be best to mention briefly the morphologic changes of the red blood-cells present to a lesser or greater degree in all forms of anemia. The abnormal red cells as they appear in the circulating blood depend on the degree of regenerative activity of the bone-marrow which, in turn, depends on the degree of anemia. The first and important morphologic change in any form of anemia is the alteration in shape and size of the red blood-cells. This is known as anisocytosis. This change is due to the extreme elasticity

of the red blood-cells. Compared with normocytes, pathologically altered sizes are encountered, some much smaller than the normal, being only 4 to 6 microns (microcytes), others larger than normal, 8 to 10 microns (macrocytes), and still others 10 to 12 microns, named by Ehrlich "gigantocytes," also known as megalocytes.

In secondary anemia the microcytes predominate, indicating exhaustion of bone-marrow function. They may also be present at a time when the germinative quality of the bone-marrow is in perfect condition, as, for instance, in polycythemia. Under very rare conditions still smaller red blood-cells are encountered in the blood which were first described by Ehrlich²² as schistocytes. These are only 2 to 3 microns in size and are an indication of the unripe products of bone-marrow. They are found in the bone-marrow in aplastic anemia, in which disease they are also numerous in the circulating blood. The macrocytes are, as a rule, rich in hemoglobin and often show a polychromatic tendency; some of the cells contain basophilic punctate. At times rests of nuclei are found in these cells (Howell-Jolly bodies). The Howell-Jolly bodies were at first considered by Ehrlich to be signs of degeneration of the red blood-cells. In reality, they are often encountered in anemia where regenerative tendency is very marked. These bodies were found to be very numerous in cats after bleeding, as first demonstrated experimentally by Howell, which indicates that they are not degenerative products of red blood-cells, but a regenerative manifestation of bone-marrow.

Clinically, it is known that large numbers of Howell-Jolly bodies are encountered in the blood after splenectomy. It is also known that they may occur in such anemias where the spleen is not diseased. The relation of the spleen to the appearance of the Howell-Jolly bodies is still subject to controversy. It is possible that there are internal secretory relations between the function of the spleen and the bone-marrow, inasmuch as the denucleation of the red blood-cells by the bone-marrow is influenced by a hormone in the spleen. It is at the same time plausible that after the removal of the spleen this hormone

function is taken up by other lymph-glands therefore the Howell-Jolly bodies may be found in the circulating blood many years after splenectomy. After venesection in animals, which causes considerable loss of blood, the Howell-Jolly bodies can be made to appear in the circulating blood.

Normoblasts may be orthochromatic or polychromatic. Orthochromatic normoblasts have the size and staining quality of normal erythrocytes and their nuclei are small. The polychromatic normoblast shows staining also of protoplasm, the nucleus being larger and the protoplasm showing a varying degree of intensity in its affinity to basic dyes. The methylene-blue in the dye may stain the nucleus so deeply as to make it look like a lymphocyte. Polychromatophilia was considered by Ehrlich an indication of degeneration of the red blood-cells. In reality it is an expression of regeneration as evidenced by the fact that it is encountered normally in the blood-making organs. Polychromatophilia occurs in the process of denucleation. It is an expression of the youthful red blood-cell.

The presence of normoblasts in the circulating blood is an indication of acute regenerative power of the bone-marrow. The normoblasts are, therefore, encountered in all anemias where there is active regeneration on the part of the bone-marrow irrespective of the etiology. Türk⁹⁵ called attention to the fact that during the chill in malaria and also as a result of bacterial and chemical toxins in the blood, normoblasts may be encountered long before the signs of anemia are clinically outspoken.

In severe anemia another manifestation of denucleation is encountered in the circulating blood usually in the form of round or oval shaped bodies which were first described by Cabot.¹³ They are also encountered in all conditions where there is marked regenerative activity of the bone-marrow, especially immediately following severe hemorrhages. The rings may sometimes dissolve into a chain of fine, azurophilic granules which are occasionally seen in severe anemia, especially in those anemias due to lead-poisoning. Another important blood change in lead-poisoning is the presence of basophilic stippling.

Reticulated cells (*substantia granulofilamentosa*): By means

of vital stain, described above, reticulated cells may be found increased to a very considerable degree. In severe anemias they may be as high as 40 per cent.

Another rare finding in the blood-cells are particles which resemble dust. These particles are termed "blutstaubchen" (blood-dust). They are considered to be due to increase of fat particles in the blood-cells, as they are found markedly increased after a meal rich in fat. In view of the fact, however, that some of these particles take a basic stain, it is quite likely that not all are due to fat particles.

Occasionally endothelial cells are encountered in the blood. This peculiar cell has an oval nucleus and elongated, drawn out, purely basophilic protoplasm. These endothelial cells in the blood are of significance, as they are encountered as phagocytic elements as is sometimes the case in subacute bacterial endocarditis. The pathologic manifestations of the erythropoietic disturbance in the circulating blood outlined above become evident, according to Naegeli, as an expression of regeneration and degeneration of the blood-making organs.

To recapitulate, we encounter the following as an expression of regeneration of bone-marrow: 1. Young cells which are normally present in the bone-marrow also in the blood of the newborn, namely, increase in reticulated filaments, polychromasia, rests of nuclei, and normoblasts. 2. A transient increase of normoblasts or even polychromasia of the basophilic punctate red cells may be encountered after severe hemorrhage or in all forms of severe anemia. This condition has been termed by Von Noorden as blood crisis. 3. Young cells which are only present in bone-marrow of the embryo are present in the circulating blood indicating very active regeneration (basophilic, punctate, megalocytes, and megaloblasts). 4. Young cells which are not present in the embryonic bone-marrow, indicating severe pathologic reaction (Cabot's rings and cells with red basophilic granules). 5. Schistocytes and microcytes. As an expression of degeneration we encounter poikilocytosis and very large pale red cells. Another evidence of pathologic changes in the red blood-cells is marked increase in their metabolism.

CLASSIFICATION OF ANEMIA

Ehrlich and Lazarus, as well as Naegeli, divided anemia into embryonic and postembryonic types, the former signifying the presence of nucleated red blood-cells; in the latter no such cells are encountered in the circulating blood. Such a division has only histologic value, but no clinical importance. The classification of the English hematologists is by far more enlightening, as it gives a clue as to the underlying disease with which the anemia is associated. Secondary anemia may thus be classified as follows:

1. Hemorrhage.
2. Alimentary.
3. Infectious.
4. Carcinoma.
5. Lead-poisoning.
6. Chronic nephritis.
7. Physical agents.
8. Chemical.
9. Pregnancy and puerperal.

Anemia Due to Hemorrhage.—Children endure the loss of blood very poorly. In adult life women endure hemorrhages better than men. Adults can lose half or even more than half of the total quantity of blood and recover. The restoration of blood volume is brought about in the following manner: The fluid of the tissues flows to the blood-vessels, replacing the indispensable liquid constituents. An actual diminution in the blood volume evidenced by emptied vessels is only encountered if the individual succumbs to severe bleeding. If he survives for a few days, the blood volume is not diminished, only the cellular elements are diminished. The first day of severe hemorrhage, on account of the diminution in the fluids, the hemoglobin and the red blood-cells may not show any marked decrease and sometimes none at all. If the fluid is increased, the hemoglobin and red blood-cells reach the lowest point. Just as soon as regenerative activity of the bone-marrow begins, nucleated red cells appear in the circulating blood and there is also a marked increase in the white cells (posthemorrhagic leukocytosis).

This posthemorrhagic leukocytosis is of great clinical importance because it often gives us a clue, particularly in internal hemorrhages, as to the recurrence of hemorrhage. With active regeneration in the blood-forming function of bone-marrow the red blood-cells increase more quickly than does the hemoglobin. The color index, therefore, remains low even at a time when the number of red cells is normal. From the prognostic standpoint it is essential to remember that an increase in red blood-cells, although there is a low color index, is a favorable omen; the reverse, on the other hand, is unfavorable. The low color index in secondary anemia, particularly that due to hemorrhage, is responsible for shortness of breath, the typical air hunger, and restlessness. Depletion of blood-vessels is responsible for the very low blood-pressure, weak heart, hemic murmurs, and sensation of sinking and actual fainting. Hemorrhage in the first few hours causes death not because of the lack of oxygen supply, but because of failure of the circulatory apparatus. The time in which the blood returns to normal depends on the severity of the hemorrhage, the relative regenerative ability of the bone-marrow, and the age of the patient. Adults recover much more quickly from the effects of hemorrhage than children. Four to six weeks is estimated as the time for complete recovery after an active hemorrhage has ceased. Continuous oozing of blood if of very long duration irrespective of how benign the cause is (hemorrhages from benign uterine tumors, menorrhagia due to ovarian disturbance, bleeding from hemorrhoids, or benign polyp of stomach) may cause loss of regenerative power of the blood-forming function of the bone-marrow, and thus a severer form of a plastic anemia. It is a remarkable clinical fact that the development of anemia after bleeding depends also upon the organ from where the bleeding originates. Repeated severe hemorrhages from the lungs and especially protracted hemoptysis seldom lead to any marked secondary anemia. On the other hand, protracted oozing from the mucous membranes, as, for instance, benign polyps of rectum, hemorrhoids, bleeding from gastric or duodenal ulcer, causes very severe anemia. It is well known how frequently bleeding hemorrhoids cause such

severe anemia that malignancy is suspected, and after the removal of the hemorrhoids complete recovery quickly takes place.

The blood-picture depends, therefore, on the duration of the hemorrhage. In the milder forms there is a marked reduction in the color index, moderate leukocytosis, and a moderate reduction in the number of red blood-cells. In the severer forms the hemoglobin may go down as low as 18 per cent. or even 15 per cent., the red blood-cells to less than 1,000,000, and the stained smear shows all forms of regenerative erythroblastic manifestations in the bone-marrow as well as regenerative changes. The regenerative changes are evidenced by the nucleated red cells and occasionally also by macrocytes and megalocytes; the degenerative changes by schistocytes and microcytes as well as the basophilic granules and Howell-Jolly bodies. Polychromatesia is, as a rule, never encountered in secondary anemia. The bone-marrow in severe secondary anemia is usually very red due to its hyperactivity. If the bleeding continues for a long time exhaustion of the bone-marrow takes place and the bone-marrow becomes yellow instead of red.

Alimentary Anemia.—Hunger in itself, even if lasting for a long time, does not cause anemia. It only impoverishes the blood and the rest of the tissues in the body. The hemoglobin and the red blood-cells are but very moderately diminished. This was demonstrated in those who have gone on a hunger strike and during the Great War. In cases where protracted hunger or improper dieting causes so-called hunger edema, evidence of secondary anemia is indicated by the low hemoglobin and reduced number of red blood-cells. These cases of anemia, however, are not so much due to destruction of the red blood-cells or the interference of the productive activity of the bone-marrow, but to the hydremia which dilutes the hemoglobin and causes relative reduction in the red blood-cells.

There is, however, a form of alimentary anemia which is caused either by the quality of the food having a toxic effect on the bone-marrow or, what is more frequently the cause, the lack of vitamins. We are all familiar with adult scurvy manifestations and secondary anemia resulting therefrom, anemia that

accompanies beriberi, the anemia in infancy first described by Czerny and his pupils, which is caused by improper feeding, and the Barlow disease in children.

Anemia Due to Infection.—Another form of secondary anemia is that due to acute and chronic bacterial, parasitic, or spirochetal infection. The acute infection may cause severe anemia only if due to *Streptococcus hemolyticus*. These organisms have such a hemolytic effect on the red blood-cells that within a few days after the onset of the disease the appearance of the patient and the blood is that of severe anemia. Anemia due to chronic streptococcic infection is best exemplified by that caused by *Streptococcus viridans* (bacterial endocarditis—Liman⁵²) or the same organism occasionally effects the gall-bladder (cholecystitis lenta of Schotmüller). The bacterial endocarditis anemia gives rise to the characteristic physical appearance (*café au lait*). The blood changes are chiefly confined to the blood-cells, namely, reduction in number of red blood-cells and considerable reduction in hemoglobin, marked hypochromatic appearance of the red blood-cells, poikilocytosis, anisocytosis, and the predominance of microcytes. In severe anemia due to bacterial infection, especially bacterial endocarditis, endothelial cells are at times encountered.

Malarial infection is practically one of the very few diseases that brings about anemia by directly damaging the red blood-cells. The blood-picture, therefore, in malaria, even before the anemia is developed, shows changes in form and in staining of the red blood-cells. The red blood-cells are often larger, stain poorly, and they show the so-called Schufner dippling. These dipplings consist of small little dots which are first round and then spread out equally over the entire blood-cell. They stain intense red with chromatin and the cellular parts lying between these little dots are pale. If the parasites grow into the blood these little dots become larger and stain even more intensely. They also entirely surround the parasite. They occur exclusively in the tertian type of malaria. In addition to Schufner dippling, coarse granules are seen in the red blood-cells in the tertian type of malaria. They are much more marked in the

pernicious type of malaria and present only in those blood-cells which harbor the plasmodii. They were first described by Brug, of Holland, and known, therefore, as *Brug spots*. Acute malarial infection, especially that due to the tertian parasite, may show in the circulating blood erythrocytes in all stages. There are often encountered nucleated red blood-cells containing parasites, poikilocytosis, and anisocytosis. Frequently there is macrocytosis. Megaloblasts are encountered in very severe cases. In chronic malaria the malarial cachexia may show very severe changes in the blood during relapses. In this stage the blood-picture may be that of anemia without any evidence of existing parasites and, therefore, the underlying cause for the anemia is determined with great difficulty. This is a great disadvantage, because in this form of anemia the treatment of the underlying cause has a very beneficial effect. Severe forms of malarial anemia which were not treated often lead to aplasia of bone-marrow with the picture of aplastic anemia minus the hemorrhages from the skin and internal organs. This is important to emphasize because in severe aplastic anemia without hemorrhage, especially if the spleen is enlarged, malaria should be thought of and treatment instituted. It should be remembered that the blood-platelets are diminished in malaria, that the specific gravity of the blood is lowered, and that there are often encountered Cabot's rings and Howell-Jolly bodies, and, what is more important, that there are basophilic granules almost always present in many of the red blood-cells. The white cells usually show mononucleosis and lymphocytosis. In this connection it must be mentioned that severe massive destruction of the red blood-cells in malaria often leads to so-called "black-water fever." The hemoglobin and the number of red blood-cells may fall to one-fifth the normal number, the spleen and liver become very much enlarged, and, on account of the enlarged capsules of these organs, there may be considerable pain over the splenic and liver regions. The clinical symptoms are those of paroxysmal hemoglobinuria.

Luetic Anemia.—In the congenital type of lues, during childhood, the enlargement of the glands and spleen with marked secondary anemia is not an infrequent occurrence. Later in

adult life luetic infections of the hematopoietic system is not quite as common. Anemia of a secondary type is encountered, especially in visceral lues, if the liver is affected by gumma. Anemia is likewise an accompaniment if other digestive organs are effected by lues, as, for instance, interstitial pancreatitis, luetic achylia gastrica, luetic organic changes of the stomach of a fibrous and gummatous type. In certain cases of cerebro-spinal lues and the late stage of tabes dorsalis evidence of secondary anemia is not infrequent. What is most important, clinically, is that at times syphilis manifests itself only in disturbance in the hematopoietic system. The patient presents the typical picture of splenic anemia. It is well known that that form of splenic anemia first described by Banti and known as Banti's disease is in the vast majority of cases due to syphilis. The blood-picture is typical of that of Banti's disease, namely, secondary anemia with predominance of monocytes.

Anemia Due to Carcinoma.—It is a clinical fact that the degree of anemia in carcinoma depends on a great many factors. Not infrequently it depends upon the seat of the cancer. Very often individuals suffering from cancer approaching death, although showing marked emaciation, still fail to show the typical picture of anemia. Even stenosing carcinoma of the stomach, with its very marked inanition, as well as stenosing carcinoma of the cardiac end of the esophagus, may show a comparatively normal blood-picture, and sometimes, even like benign pyloric stenosis, there may be a relative polycythemia because of the excessive loss of fluids. Malignant tumor of the lung, pleura, and bronchi may be present without any manifestations of anemia.

On the other hand, cancer of the cecum, as first pointed out by Mayo, gives rise very early to severe anemia. This is also true of scirrhus carcinoma of the stomach and especially carcinoma of the pancreas. What are the factors in carcinoma which bring about anemia? Can we be guided by the presence of anemia as to whether the cancer is operable? It is not infrequent that the cachectic and anemic appearance of the patient suffering from cancer of the stomach or colon would make us

feel that operation is not advisable, and still, if it can be demonstrated roentgenologically that the cancer is situated in an operable zone and if the patient is transfused, the cancer may be removed and the patient may make a complete recovery. In such a case the patient may go on for years. The anemia due to cancer depends on a number of factors. In the first place, it depends on the bleeding of the cancer. In advanced cases of carcinoma of the stomach or colon the hemorrhage is, as a rule, profuse, due to erosion of large vessels, and is usually rapidly fatal even if blood transfusion and surgical intervention are resorted to. If the cancerous area in the stomach or colon causes slow oozing the anemia may be very severe and still be favorably influenced by blood transfusion and surgical intervention. There may be anemia in carcinoma due to irritation of the hematopoietic system resulting from toxins evolved by the new growth. In such cases the appearance of the patient and even the blood-picture may sometimes simulate pernicious anemia. There are, however, some distinguishing characteristics even in the blood which make a differential diagnosis possible; the color index in anemia due to carcinoma with bone-marrow irritation is almost always below one; microcytosis predominates and macrocytes even if present are only few in number; hyperchromasia is absent; the blood-serum is pale and does not give the indirect Hijman-Van den Bergh reaction, and the duodenal contents do not contain an excess of bile-pigment. There is also, as a rule, no considerable increase in urobilin in the urine. The teaching that urobilin in the urine is an indication that there is metastases in the liver and therefore contraindication to surgical intervention, was proved by Matthes to be incorrect. He showed that in some cases where metastases to the liver was present there was no urobilin; on the other hand, urobilinuria was present without metastases to the liver.

There is still another form of anemia due to cancer in which the bone-marrow is directly involved by metastases. This anemia occurs in hypernephroma, malignant tumor of the thy-roid, mammary gland, lungs, prostate, and sometimes pituitary gland. In these cases the anemia is unusually severe and the

symptoms of bone involvement so outspoken as to mask the primary seat of the cancer simulating primary tumors of the bone (multiple myeloma) in which the anemia is an early symptom. Differential diagnosis between metastatic bone tumor and primary bone tumor can be made by the presence of Bence-Jones bodies in the urine in the latter disease.

Chronic Nephritis.—Secondary anemia is often present in chronic nephritis with and without edema. The blood-picture in nephritis with edema shows the signs of secondary anemia; the hemoglobin and red blood-cells may be markedly reduced, which in part may be due to the presence of hydremia. Anemia in secondary contracted kidney also shows the blood-pictures of secondary anemia, although Berg encountered cases of secondary contracted kidney in which there was a high color index. Anemia in this form of nephritis is, without question, of toxic origin.

Anemia Due to Intestinal Parasites.—*Bothriocephalus latus* and *Ankylostoma duodenalis* are the parasites which may cause severe anemia; the former brings about the clinical picture resembling strongly pernicious anemia as far as the changes in the red blood-cells are concerned and also causes achylia gastrica. It never causes any changes in the spinal cord. Anemia due to intestinal parasite has an additional blood characteristic not encountered in pernicious anemia, namely, the presence of eosinophilia.

Anemia Due to Physical Agents of Blood.—Ever since *x*-ray treatment and radium have been actively used cases of severe secondary anemia have been reported as a result of such treatment. As a rule, the deleterious effect of *x*-ray is mostly on the white cells, bringing about some form of leukemia. Under rare conditions the red blood-cells are affected. If the red blood-cells are affected, they cause poikilocytosis and anisocytosis and even a severe form of aplastic anemia with fatal termination. What is true of the *x*-ray is to a lesser degree true of radium.

Chemical Poisons Causing Hemolytic Anemia.—All poisons which have hematoxic properties and those which chemically disturb the hemoglobin have but little clinical significance be-

cause human beings rarely come in contact with such poisons. This is true of potassium chlorate unless accidental poisoning by an overdose occurs, and phenylhydrazin (although of late phenylhydrazin has been advised in polycythemia), if not used with great caution, is liable to lead to marked hemolytic anemia. We had occasion to see an autopsy where phenylhydrazin was used in polycythemia. Death resulted twenty-four hours after the administration of the drug. The liver was completely destroyed. Saponin likewise is seldom encountered as a cause of human anemia. In occupational diseases, on the other hand, nitrobenzol and tolualenediamin may be the cause of severe secondary anemia. Poisoning with hydrogen sulphid is an important factor in secondary anemia. The oxygen is replaced in the hemoglobin by sulphmethemoglobin or cyanmethemoglobin, which can be demonstrated spectroscopically or even by the reddish-brown color of the blood. In very severe chemical poisons the red blood-cells are destroyed, the coloring-matter enters the blood-plasma, and from there into the urine, causing methemoglobinuria. This occurrence damages the parenchyma of the kidneys severely. Very active reparative manifestations takes place in the bone-marrow.

Anemia resulting from chronic lead-poisoning has special diagnostic blood characteristics. In addition to the blood changes characteristic in all forms of secondary anemia, the basophilic punctate of the red blood-cells is very marked.

This change in the red blood-cells was first brought to our attention by Grawitz.³⁰ After Grawitz had first described this condition, active discussion began as to whether these punctate basophils are the result of regenerative or degenerative manifestations in the bone-marrow. Experimental studies proved that it is a regenerative phenomenon. It is interesting to note that anemia due to acute and chronic lead-poisoning, if the lead exceeds a certain dose, these basophilic granules disappear. Other blood manifestations of lead anemia are very few. The number of basophilic red blood-cells is variable. The highest number is about 42 per cent. The reduction in hemoglobin and red blood-cells in lead anemia is, as a rule, not very marked, al-

though in rare cases the hemoglobin may be as low as 50 per cent. and the red blood-cells below 4,000,000.

Another important blood-poison causing marked changes in the hematopoietic system is carbon monoxid. The carbon monoxid poison has 200 times more affinity for hemoglobin than oxygen. The blood damage by the lack of oxygen stimulates the bone-marrow to active erythrocytosis.

Pregnancy and Puerperium Anemia.—Anemia may occur in the course of pregnancy and puerperium. Osler⁷¹ classified these anemias as follows:

1. Anemia secondary to postpartum hemorrhage.
2. Severe anemia of pregnancy which may show the characteristics either of secondary anemia, pernicious anemia, or aplastic anemia.
3. Postpartum anemia.
4. Acute anemia as a result of puerperal sepsis.

Larrabee⁴⁹ reported 17 cases of anemia occurring in pregnancy and puerperium. Seven of the cases showed the blood-picture of secondary anemia, and all of them recovered. Eight cases presented the pernicious blood-picture. Four recovered after transfusion. Of the 4 cases that were not transfused, 3 died. One case of aplastic type died in spite of transfusion. Repeated transfusions were not successful. A highly atypical case recovered after splenectomy. The etiology of these anemias is obscure. Some attribute them to the damage wrought on the hematopoietic organs by hemorrhage and infection. Adler believes that all the anemias of pregnancy occur in women who are predisposed or who are already suffering from some other form of anemia, especially chlorosis, posthemorrhage, or secondary anemia. In such women the added strain of pregnancy upon the blood-forming organs results in pathologic conditions of greater or less severity and of varying types. The theory of Hofbauer, quoted by Rolland,⁸⁰ is the following: Syncytial hemolysin is produced in the ectodermal cells of the chorion. Later on an antihemolyzin is formed in the maternal blood which accounts for the disappearance of slight anemia so frequently observed in the early months of normal pregnancy. If such antibodies fail, a destructive anemia persists. Correl and Ebling,¹⁷ in a study of

the growth of the fibroblasts in the serum of old animals as compared with that of young ones, found evidence that the serum in adults contains some factor which inhibits cell growth. On the basis of these findings, Calloupe and O'Hara²⁷ suggest that parturition may interfere with the blood-forming tissues as a result of some substance produced from the fetus and that progressive anemia might result if the hematopoietic mechanism fails to compensate. McQuarrie²⁶ considers it possible that the hemolytic anemia of pregnancy has many points of resemblance to toxemia and many connections with the same causes. Larrabee is correct when he states that the theories enumerated are only suggestive, and must be regarded rather as leads for further study than as lucid and satisfactory explanations of clinical facts.

Primary Anemia.—The group to be discussed now is still in the dark as far as the etiologic factor is concerned, and hence it is termed "primary anemia." Naegeli divides anemias, where the underlying etiologic factor is still unknown, into constitutional, hereditary, and conditional anemia. The constitutional hereditary anemia is represented by the hemolytic form with and without icterus, and with and without enlargement of the spleen, by chlorosis and by pernicious anemia. Conditional anemia is such primarily where there is no constitutional tendency to anemia, but pathologic changes occur in certain organs which prepare the soil for development of anemia. This is exemplified by anemia occurring in the course of myxedema and that of Addison's disease. Both constitutional and conditional forms of anemia may in addition to the endogenous underlying factors also have exogenous exciting factors. The symptoms of hemolytic icterus, for instance, which is a constitutional hereditary anemia, are markedly aggravated, and hemolytic crisis is often induced as a result of infection or even mental shock.

HEMOLYTIC ICTERUS

This disease has clinical interest because it occurs frequently and because of the favorable therapeutic results obtained by splenectomy. As is well known, Minkowski was the first who described this symptom complex under the name of "familial

hemolytic icterus" because it frequently occurs in several members of the same family. Naegeli named the disease "constitutional hereditary hemolytic icterus." The name constitutional hereditary hemolytic icterus is appropriate. Naegeli mentioned a village in Germany of 900 inhabitants, where, on account of intermarriage, 20 per cent. of the inhabitants were afflicted with the disease. Eppinger believes that this affliction is etiologically related to pernicious anemia. This, however, cannot be accepted because both diseases have only one factor in common, namely, the evidence of hemolysis, otherwise they are symptomatically as well as prognostically entirely different. Naegeli is of the opinion that hemolytic icterus is caused by a disease of the spleen (hypersplenism) which causes marked destruction of the red blood-cells. This theory is also not accepted. The theory of Morawitz is more plausible. He states that the disease is caused by an inferiority in the quality of the erythrocytes which accounts for the fact that they are destroyed in the spleen and by phagocytosis in the reticulo-endothelial cells. In these cells the broken-down red cells are converted into bilirubin to such an extent that they cannot be stored in the liver, so some of it enters the blood, causing icterus.

The disease is clinically recognized in most cases by a moderate icterus which occurs early in adult life. During childhood the icterus may not be evidenced at all. The yellowish discoloration is confined chiefly to the sclerae. The skin appears pale, grayish in color. In severer cases the face resembles somewhat pernicious anemia. Naegeli states that the head is peculiarly shaped in this disease, an observation which has been confirmed by many authors. The forehead protrudes and is steep in appearance, giving the head a tower shape. This is again an indication of constitutional hereditary nature of the disease. There may not be any other symptoms, and hence Chauffard correctly stated that the patient is more yellow than sick. It is characteristic that these individuals, even during the so-called symptom-free period, tire readily and are frequently subject to gastric upsets with pain over the liver region. This pain may sometimes be so severe as to simulate gall-stone colic. In some

cases actual gall-stone colic takes place which is undoubtedly due to the excess of bile-pigment in the liver cells. The stones in the gall-bladder in these cases are of the bilirubin type. Objectively there is, in addition to the anemic appearance, the presence of the peculiarly shaped skull and enlargement of the spleen which is hard in consistency and of varying size. The examination of the blood is very important in this disease. The serum is brownish yellow due to the increase of bilirubin, especially the indirect bilirubin (Hijman-Van den Bergh). The resistance of the red blood-cells is markedly diminished. This phenomenon characterizes this form of anemia from all other forms. The examination for the resistance of the red blood-cells is very simple and can be carried out in the office. It is known that normally the hemolysis of the red blood-cells begins in hypotonic solution of 0.55 or even as low as 0.28. In hemolytic icterus hemolysis in a hypotonic sodium chlorid solution may occur at 0.7 or 0.6. The test is carried out by placing 25 drops of 0.5 per cent. sodium chlorid solution in the first tube, 24 drops in the second, and one less in each succeeding tube than in the one immediately to the left of it. No distilled water is added to the first tube, but in the second tube 1 drop, in the third 2 drops, and so on until the total number of drops of sodium chlorid solution and distilled water is 25. Blood is obtained from the person's veins and 1 drop of the blood is added to each tube of hypotonic salt solution. At the same time, for control, there is placed in a similar number of tubes blood from a person without jaundice. In any other form of icterus (catarrhal or that due to biliary stasis) the resistance of the red blood-cells is increased. The hemoglobin is usually moderately reduced in most cases to 70 per cent., and the red blood-cells may be about 3,000,000 or 3,500,000. The color index is 1, and sometimes lower. The stained specimen shows polychromatasia, a very marked increase in the reticulated filaments, and a striking microcytosis. The urine is usually darker in color because of the excess of urobilinogen and urobilin. It never contains bilirubin unless complicated by transient common duct obstruction. The stool contains an excess of bile-pigment and is, therefore, much darker than normally. Because the

stool is never acholic the disease has also been termed "acholuric icterus."

The clinical picture as well as the blood-picture changes considerably during the periods of blood crises. Such crises may be brought about by physical and mental overstrain. The mental overstrain is probably more responsible for the crisis than the physical overstrain. During this stage the anemia as well as the icterus becomes much more pronounced. Actual deep icterus never exists. Itching of the skin is likewise absent. This is attributed to the fact that the bile acids in the blood are not increased in the disease. The pulse is also not slow. The hemoglobin during the crisis may go down to 40 per cent. or less with a corresponding decrease in the red blood-cells. During this stage the color index is always above 1. The reticulated filaments are markedly increased. Polychromatosis and microcytosis are marked features. Whitcher¹⁰⁰ studied the blood-picture before and after splenectomy in hemolytic icterus. There was a return to the normal blood-picture and a very distinct improvement in the corpuscles after the operation. There is a disappearance of the microcytes after splenectomy, in contrast to their abundance in the blood before operation. This feature may be regarded as a concomitant manifestation of anemia rather than an inherent character of erythrocytes of the individual. Normoblasts may be present. Megaloblasts and macrocytes are very seldom encountered. Chauffard and Hayem describe a similar clinical picture under the name of "acquired hemolytic icterus" occurring later in adult life and having some of the clinical characteristics, namely, the enlargement of the spleen, the pseudo-gall-stone colic, moderate enlargement of the liver, urobilinuria, but no bilirubinuria, and an increase in the indirect bilirubin in the blood-stream. •It differs, however, from the constitutional hereditary type by the fact that the resistance in the red blood-cells is very frequently not altered. The color index is, as a rule, below 1 and microcytosis is not very marked. The reticulated filaments are also never increased to the same degree. This acquired form is, in reality, a secondary affection, and may be encountered in thrombosis of the portal vein as a result either of

chronic intoxication or lues, also where there is a breaking down of the red blood-cells as a result of Roentgen treatment or other blood poisons, especially excessive use of iodids. Such a clinical picture has been caused by large doses of potassium iodid or by x-ray. The prognosis of the Minkowski type is, as a rule, favorable. If repeated blood crises occur splenectomy ought to be advised. In some cases the frequent attacks of gall-stones may necessitate cholecystectomy long before splenectomy. The acquired form does not yield as favorably to splenectomy as the inherited form. Dr. Kanner in a personal communication states that he found hypocholestolemia in hemolytic icterus before splenectomy and a hypercholesterolemia following it. He is of the belief that the cholesterol protects the integrity of the red cells and is working on a cholesterol compound by mouth to increase the cholesterol content of the blood which he hopes will replace splenectomy.

Sickle-cell anemia bears certain resemblance to hemolytic form of anemia and, although it is a very rare disease, it deserves brief discussion.

In 1910 Herrick³⁶ first called attention to a peculiar change in the shape of the red blood-cells in a severe case of anemia. He described these erythrocytes as assuming an elongated or sickle shape. Since that time Washburn,⁹⁷ Huck,³⁹ Emmel,²³ Anderson,³ and others described the same changes in the shape of the erythrocytes in certain severe cases of anemia. The distortion of the red blood-cells are so constant that the name sickle-cell anemia is appropriate.

The etiology is practically unknown. Sydenstricker, Mulberin, and Houseal⁹⁴ state that the blood dyscrasia is transmitted according to the Mendelian law and manifests itself as a dominant characteristic. The cases thus reported have all been limited to the negro race. The same authors also point out that this anemia is particularly frequent in the Detroit negroes. Huck states such cells may also be associated with anemia of the hemolytic type. These cases Huck terms "sickleemia." Dreyfus²⁰ states that such cases have been observed in newborn negroes.

Symptoms.—Sydenstricker divides the symptoms into two

phases—active and latent. During the active phase the anemia is most pronounced. The scleræ have a greenish discoloration. The tonsils are hypertrophied and there is a general lymphadenopathy, but there is no enlargement of spleen. The case of Anderson showed in addition to this marked mental disturbance. During the latent stage all symptoms may disappear except that the sickle cells are present in the blood. The peculiar shape of the red blood-cells is observed best in fresh blood preparations which have stood for twenty-four hours. The bone-marrow shows evidence of hyperplasia and striking changes in the shape of the red blood-cells. The liver is large and shows deposits of a brown iron-free pigment. Large phagocytes are present in the spleen and blood-stream. The progressive anemia, in case of bilirubin in the blood, pigmentation of tissues, and urobilinuria are an indication of active blood destruction. It may be mentioned here that among the anemias of hemolytic group Gordon Ward⁹⁶ describes the Dreshack's syndrome, where there is anemia with elliptical red cells, Malin's syndrome of phagocytic anemia or auto-erythrophagocytosis, and Clough and Richter's syndrome, where, in addition to the anemia, auto-agglutination of the red cells take place.

PERNICIOUS ANEMIA

Pernicious anemia is one of the most severe affections of the blood resulting from a disturbance in the erythropoietic system. There is still much discussion as to whether the name "pernicious anemia" is appropriate. Hurst¹² prefers to call it "Addison's anemia" because Addison was the first to describe the disease. The German school adheres to the name "Bierner-Ehrlich's anemia" because Bierner furnished the most exact clinical description and Ehrlich contributed so much to the hematologic study of the disease. I believe that the name pernicious anemia is appropriate, and in those cases where the etiology is unknown the disease may be named "essential or cryptogenetic pernicious anemia"; whereas in those cases where the etiologic factor is known, the name anemia plus the causative factor may be applied, as, for instance, bothriocephalus anemia, pregnancy anemia, etc.

Etiology.—Since Hunter⁴¹ expressed the view that oral sepsis, of which he considered glossitis to be a part, is most likely responsible for pernicious anemia, untiring efforts have been made to demonstrate the relation of infection or toxins of the gastro-intestinal tract as causative factors in pernicious anemia. There the toxins may take their origin in either bacteria or foreign proteins.

In 1906 Herter⁴⁷ reviewed his numerous observations on the bacteriology of the gastro-intestinal tract in advanced anemia and furnished important proof that *Bacillus welchii* was a cause of pernicious anemia. He noted that in many individuals afflicted with pernicious anemia the gastro-intestinal tract showed the presence of greatly increased numbers of anaërobic gas-making bacilli identical with *Bacillus welchii*. Herter believed that the chemical products from these bacteria would account for the symptoms of pernicious anemia. He further noted that in certain cases of advanced anemia, if the blood-picture and the general condition improved, there was a distinct reduction in the number of *Bacilli welchii* in the feces with a marked increase of colon group bacilli. Herter also noted a close association between certain anemias and capsulatus infection of the gastro-intestinal tract. This work stimulated clinicians and bacteriologists to study pernicious anemia in relation to bacteria. Kahn and Torrey⁴⁴ injected a toxin from cultures of *Bacilli welchii* into monkeys and produced changes in the blood strongly suggestive of pernicious anemia. Cornell¹⁶ has also obtained similar results by instituting a chronic infection with *Bacillus welchii*.

Hurst and Bell⁴⁸ believe that infection of the gastro-intestinal tract is a cause of pernicious anemia. Because the antiseptic action of the normal gastric juice is absent in pernicious anemia, the bacteria which reach the stomach can pass into the intestines and thrive there. Hurst and his co-workers found an abundance of *Streptococcus longus* in the duodenal contents, the toxins of which they believe to produce the various lesions in pernicious anemia. The hematoxin causes the hemolysis in the blood, bringing about the characteristic blood-picture, the neurotoxin causes the subacute combined degeneration of the cord, and a third

toxin acts on the bone-marrow. Percy found bacteria in the liver, spleen, and gall-bladder in pernicious anemia.

The studies of Seyderhelm⁸⁸ are very interesting in connection with bacterial toxins as a cause of pernicious anemia. This author demonstrated experimentally that the toxins of the coli group from the intestines can, if injected into an animal intravenously, produce the typical blood-picture of pernicious anemia. The toxin is prepared from the cultured bacteria obtained from the feces of such patients. If the extract is given to the animal by mouth, negative results are obtained. Seyderhelm also obtained similar toxins from the mesenteric lymph-glands of patients who died from pernicious anemia. Like Hurst, he is of the opinion that achylia gastrica is an important factor because it gives the coli group an opportunity to thrive in the small intestine. On the basis of his findings, Seyderhelm advocates exclusion of the colon as a therapeutic measure. Three of the 5 cases which were so treated for pernicious anemia by Seyderhelm showed marked improvement. The toxin reaches the circulation through the intestinal wall, and although most pathologists, including Sheard, never found any pathologic changes in the intestinal wall, Seyderhelm states that no macro- or microscopic lesions of the gastro-intestinal tract need be demonstrable, and still minute lesions may exist which would allow the toxin to pass through. Seyderhelm obtained a *Bothriocephalus latus* toxin which he named "bothriocephalin." He injected this bothriocephalin into animals intravenously and a typical picture of bothriocephalus anemia developed. These toxins do not act *in vitro*, but only when introduced directly into the blood. According to Seyderhelm, even the pernicious anemia in cancer has its underlying basis in the achylia which has an injurious effect on the small intestine, making it possible for bacterial toxins to pass through and injure the bone-marrow. Anemia occurring in lues and sprue is also considered by Seyderhelm to be due to the existing achylia. That carcinoma may simulate pernicious anemia is well known, and the close clinical resemblance of pernicious anemia to carcinoma even to the point of simulating cord symptoms is illustrated in a case recently published by Garvey

and Stein.²⁸ In their case there was posterolateral degeneration of the spinal cord associated with carcinoma of the stomach. The degeneration of the cord was not due to metastases, but was typical of subacute combined degeneration of the cord encountered in many cases of pernicious anemia, according to Woltman in about 80 per cent. of the cases. Association of sprue with pernicious anemia has recently been carefully studied by Musser.⁶⁹

The causative relation of foreign protein toxins to pernicious anemia was demonstrated experimentally by Cederberg.¹⁵ He is of the opinion that if the intestinal mucosa is not intact in man, foreign proteins may produce similar anemia. Eppinger²⁴ suggests that an increase of unsaturated fatty acids of the blood might be a responsible factor for this which can be demonstrated in certain diseases in which hemolysis is a characteristic feature including pernicious anemia. Bothriocephalus anemia, according to some authors, is brought about by fatty acids contained in the parasite. It is known, however, that severe anemia, even of a pernicious type, may sometimes be present as a result of other intestinal parasites in which no fatty acids are found. The diminution in the amount of lipid in the suprarenal cortex often found in individuals who died from pernicious anemia suggests the possibility that there is some abnormality in the function of the suprarenals. The low blood-pressure, the diarrhea, the brown patches of the mucous membrane of the mouth in pernicious anemia are attributed to a disturbed suprarenal function. Scott⁸⁶ and Lindemann demonstrated experimentally that the injection of 5 c.c. of blood from a healthy person or from patients with polycythemia, secondary anemia, nephritis, bacterial endocarditis, icterus, or pernicious anemia into a guinea-pig weighing 1500 grams the effect on the animal is exactly the same. The animal succumbs eventually with the symptoms of a moderately severe hemoglobinuria, but the number of red blood-cells remains unchanged. If on the third or fourth day after the first injection, namely, before the anaphylactic stage sets in, a second injection of blood of 5 or 10 c.c. from a normal human being is given, a mild shock with moderate hematuria occurs, but no change in the red blood-cells. This is also true if the blood is obtained from

patients afflicted with the above-mentioned diseases with the exception of pernicious anemia. If the blood from a patient suffering from pernicious anemia is injected the second time, the guinea-pig develops all the blood changes as well as signs of hemosiderosis. The conclusion drawn from this is that there is a toxin in the blood of a patient afflicted with pernicious anemia which prepares the soil for further destruction of the blood.

Notwithstanding the above experimental work, it must be stated that the exact etiology is still unknown, and that even the known factors, such as bacterial toxins and foreign proteins, are most likely only contributory. If these were the actual causes, pernicious anemia would be a much more frequent disease. It is well known that toxins of all bacteria including the coli group are present in a large number of people and may even give rise to symptoms, but still not cause pernicious anemia. The same can be argued regarding the toxin of *Bothriocephalus latus*. In Scandinavia, particularly Finland, where the number of individuals afflicted with tapeworm is very great, only a small number suffer from pernicious anemia. This is also true of pernicious anemia occurring in cancer, lues, and even in achylia gastrica. Even those authors who assume that achylia gastrica is a predisposing factor, state that in only 7 per cent. pernicious anemia resulted. Even these statistics cannot be taken seriously because a large number of people go through life with achylia without any symptoms, and therefore are never examined by physicians. While it is true that lues, pregnancy, puerperium, sprue, and *Bothriocephalus latus* predispose to subacidity or even to achylia, it is equally true that in *Bothriocephalus latus* pernicious anemia free acid was found in about 50 per cent. of the cases. Naegeli, Lichty, and others reported cases of typical pernicious anemia, although free acid was present. From what was stated above it must be concluded that even if this is a demonstrable cause, it serves only as a contributory factor, whereas the real underlying cause is undoubtedly hereditary. Most authors agree that heredity is a causative factor. Schaumann,⁸² Cabot, Hale White, Matthes, and others reported cases where a few members of one family were afflicted with the disease. Barlett⁷ reported a

history of a family living in Vermont in which the father died at forty and a son at twenty-four from anemia. There was no blood examination. As no other obvious cause of death was found at autopsy, it seems quite likely that the deaths were due to pernicious anemia. Two other sons out of a total of 5 children died of pernicious anemia, the diagnosis being confirmed hematologically and by postmortem examination. Matthes reported the occurrence of the disease in three members of one family. Levine and Ladd⁵¹ investigated the family history of 143 cases of pernicious anemia and obtained definite proof that the disease existed in 9 members of the family. In Cabot's series of cases the disease occurred twice in two sisters and once in a brother and sister. Such a constitutional factor may, according to Barker,⁶ be inherent (genotype) or acquired (paratype). Where there is such constitutional inferiority as a predisposing factor, other contributory factors, such as pregnancy, chemical toxins (lead, phosphorus, etc.), chronic infections, especially lues, may lead to the typical picture of pernicious anemia. If we accept the constitutional factor as a primary cause it is easily understood why some cases of pernicious anemia may progress from an ordinary secondary anemia or understand why symptoms of secondary anemia may be present early in pernicious anemia (Lichty,⁵³ Pappenheim⁷⁴). The almost constant presence of achylorhydria in pernicious anemia is likewise a sign of constitutional anomaly. In 1913 Faber²⁵ brought forth the first conclusive proof that the achylorhydria is primary and not secondary in pernicious anemia. He described 3 cases in which the blood was normal, the hemoglobin being 90 per cent. and more. Ten, seven, and three years later typical pernicious anemia developed. Since Faber's first publication a number of other authors reported similar cases. Levine and Ladd reported cases in which achylia existed for six years and one year respectively before the onset of anemia. They found achylorhydria with a hemoglobin of 80 per cent. and in 1 case the hemoglobin was even 104 per cent. Achylorhydria following gastrectomy has been reported to bring about at times pernicious anemia. Hartmann³⁴ of the Mayo Clinic reports a case

of a patient fifty-eight years of age who had a gastrectomy done for carcinoma of the stomach. This patient did well for about one year and then became progressively weaker and more anemic, and finally developed the typical picture of pernicious anemia. Hurst was told of 3 cases following gastrectomy for carcinoma in Vienna. Since subtotal gastrectomy has been practised for gastric and duodenal ulcer cases have been already recorded where the resulting achylia brought about pernicious anemia. It seems to me that in cases of pernicious anemia where the artificial achylia gastrica caused by gastrectomy was responsible for the disease, there must have been an inherited constitutional inferiority in the erythropoietic system, and that the achylia caused by the gastrectomy was only a contributory factor. Michmann and Zinsser⁶¹ describes a case of pernicious anemia which was caused by stricture of the colon.

"Muelengracht⁶⁵ described a case of myxedema presenting symptoms and blood-picture of pernicious anemia. The only differentiating characteristic feature in favor of myxedema was the low basal metabolism and the tense edema of the lower extremities instead of the pitting edema in pernicious anemia."

The disease is usually most frequent between the ages of thirty-five and sixty. Cabot collected 1071 cases; of these, 149 were under the age of thirty-six; not less than 922 were above forty and nearer to sixty. Very few cases have been reported before the age of ten years. The disease occurs with equal frequency in both sexes.

Pregnancy pernicious anemia usually disappears after delivery. In most of these cases the disease may not recur, but in some fatal pernicious anemia may develop even years later. During pregnancy the disease is undoubtedly caused by toxins resulting from diseased placenta because it usually occurs somewhat late in pregnancy—in about the fifth or sixth month. In most cases the placenta is definitely diseased. Severe anemia almost resembling pernicious anemia is often encountered in pregnant women afflicted with valvular disease, particularly mitral stenosis and also secondary contracted kidney. These

also result from the hemolytic action brought about by a diseased placenta.

Symptoms.—Some authors attempt to describe early symptoms of pernicious anemia. Intermittent Hunter's glossitis is the most characteristic early symptom. Glossitis causes burning of the tongue which often involves the entire mouth. Sometimes small reddish areas or even vesicles at the tip and the sides of the tongue are seen. The entire tongue and mucous membrane of the mouth may be red and angry looking and show the presence of small vesicles. The teeth are usually decayed and pyorrhea is present. At times diarrhea may be an early and troublesome symptom even before the characteristic symptoms of pernicious anemia set in. This is, however, rare. As rightfully stated by Cabot, the patients either ignore the early symptoms or consult physicians when the disease is well advanced. During this stage the color of the face is the most striking feature. It is puffy and pale yellow in color. At times the yellowish tint predominates to such an extent that it almost suggests the existence of jaundice. In these cases the scleræ are also yellowish. This is due to an increase of bilirubin in the blood which usually disappears during remissions when the color of the skin changes. On very few occasions whitish pallor of the skin may be present. The skin is usually dry and the hair brittle. Where there is a tendency to hemorrhagic diathesis small petechiæ are sometimes encountered scattered over the skin. Hemorrhages into the retina occurs quite frequently and serves at times to help in the differentiation from carcinoma. At times even ecchymotic areas are present. The adipose tissue is well preserved in the majority of cases. In some patients there is not only no loss of weight, but there may be even an increase in weight. The pulse is usually rapid and the blood-pressure low. There is marked jugular and epigastric pulsation, and in a very large number of cases there is a systolic murmur heard over the apex and pulmonic region. This murmur may be loud and even diffuse, and if, as is very often the case, there is elevation of temperature, it may be mistaken for infectious endocarditis. In Cabot's series diastolic murmurs were heard in 9 cases. Schaumann also en-

countered a diastolic murmur in 2 of his cases, although the aortic valve failed to show any pathologic changes at autopsy. Cabot, as well as Schaumann, found in some cases a presystolic murmur without any demonstrable pathologic lesion at autopsy. Persistent bruit over the jugular vein is very common. The heart may be enlarged. Fr. Kraus⁴⁶ found roentgenologically in a great number of cases typical mitral configuration of the heart. In some cases the heart may be so enlarged to the right and left that it stimulates a mitral and tricuspid insufficiency. One of the most characteristic symptoms of the respiratory organs is shortness of breath on slight exertion. This is due to the marked reduction in hemoglobin. In those cases where the disease progresses very slowly even a marked reduction in hemoglobin does not cause severe dyspnea.

The next most important symptom is that relating to the nervous system. According to Woltman, of the Mayo Clinic, there is evidence of subacute combined degeneration of the cord in over 80 per cent. of the cases. This is characterized by spastic gait, increased knee reflexes, ankle-clonus, and Babinski. In some cases the symptoms of changes in the posterior column of the cord predominate, causing tabetic gait and loss of knee reflexes.

The gastro-intestinal symptoms in addition to the above mentioned intermittent glossitis are very important. The patient complains of absolute loss of appetite, distress in the epigastrium, and diarrhea alternating with constipation. The most important objective symptom is the presence of achylia. Like Levine and Ladd, Hurst, and many others, I am of the opinion that achylia is the most constant symptom, and in case there is free acid in the gastric contents the diagnosis of pernicious anemia is very doubtful. The liver is enlarged in the majority of cases. At times obstinate constipation predominates. Diarrhea, if present, may or may not be associated with intestinal colic. The stool is usually very rich in bile-pigments due to extensive hemolysis and also contains excess of urobilin. There is usually tenderness over the long bones and occasionally over the sternum. Thrombosis of the veins in pernicious anemia is al-

most unknown because of the diminution of the blood-platelets in this disease.

The urine contains large quantities of urobilin, and is, therefore, high colored, sometimes very dark, especially if allowed to stand. In addition to this albumen may be present in large quantities. Hematuria is very rarely present. Hemoglobinuria was present in a case observed by Rudolph Schmidt. A very important objective finding, as first pointed out by Eppinger and Schneider, is the increase of bilirubin and urobilin in the duodenal contents.

Very important in the diagnosis of pernicious anemia is the tendency to remission, during which period all the subjective symptoms disappear. The blood-picture may become normal, but the achylia gastrica and the nervous symptoms, if present, may persist. A remission may last for several years, and there may be two or even three remissions during the course of the disease. According to Fr. Kraus, symptoms of pernicious anemia which set in after the second remission usually progress to a fatal termination. The duration of the disease may vary. There are cases on record where the disease lasted as long as thirteen years.

Blood Changes.—The total quantity of blood and its protein content are diminished and its specific gravity is lowered. When pricking the finger for blood, the blood is obtained with difficulty, but when the flow begins, it continues much beyond the normal time, sometimes as long as fifteen to twenty minutes due to diminution in blood-platelets. The coagulation time is not interfered with as a rule. The serum is dark brown in color. In other anemias the serum is almost white. This dark serum is due to the excess of bilirubin hematin. The reduction in red cells is out of proportion to that of the hemoglobin, and therefore the color index is high in the greatest majority of cases. The stained red cells are hyperchrome. Unlike normal red cells, where the stain is not equally distributed and there is usually an unstained bright zone, in pernicious anemia the entire red cell may be covered with the stain. Low color index in pernicious anemia is very rare or may be present only intermittently, or as a result of complications such as excessive bleeding or inter-

current infection. There is a predominance of macrocytes in contradistinction to other anemias where the microcytes predominate. Anisocytosis and poikilocytosis are marked. Macroblasts and normoblasts are occasionally found. Only a small number of microcytes and schistocytes are encountered. Other signs of regeneration of the blood, such as basophilic punctate, Cabot's rings, Howell-Jolly bodies, are often encountered. Rouleaux formation of red blood-cells is disturbed early in the disease. Leukopenia is the rule unless some infection sets in. Immature white cells are often encountered in the blood. A careful study of the blood findings with particular reference to icterus index was made by St. George and Brown.⁹² They showed definitely that the icterus index is a distinct clinical aid in separating the severe types of anemia when these anemias are not complicated by cardiac insufficiency, biliary sepsis, or pneumonia. Whitley and Jackson¹⁰¹ found phagocytes and erythrocytes in the aplastic type of anemia. Peabody and Broun⁷⁵ described phagocytes and erythrocytes in the bone-marrow in pernicious anemia. They also found phagocytes in cirrhosis of the liver and some infections, but most marked in pernicious anemia.

Treatment.—Although there is no specific treatment, most authors rightfully pay attention to the gastro-intestinal tract. The achylia should be treated, as advocated by Shaw,⁸⁹ recently again by Dorst,¹⁸ with large doses of dilute hydrochloric acid, as much as 30 to 60 mm. in a glass of water, part of which is to be taken before, part with, and part after the meal. This treatment is advocated even when the achylia is present without pernicious anemia as a prophylactic measure. Grawitz advised colonic irrigations and at times also gastric lavage in addition to the other treatment. Hurst suggests the employment of autogenous vaccine from the *Streptococcus longus* obtained from the duodenal contents. As to the dietetic régime, Grawitz is of the opinion that diet poor in proteins would be preferable because of the existing achylia. Minot and Murphy⁶² advise on the basis of experimental studies a high protein diet which is also rich in iron. They also advise an abundance of fruit, fresh vegetables, and liver in the diet. They restrict the intake of

fat. Whipple, Hooper, and Robscheit⁹⁰ advocate the intake of liver even in secondary anemia. Splenic extracts and bone-marrow have also been advised. The most important part of the treatment is blood transfusion, which must be repeated, and the direct method is preferred. Arsenic in the form of Fowler's solution, 10 mm. three times a day in increasing doses until $\frac{1}{2}$ a teaspoonful may be given. If the stomach is irritable the arsenic may be given in the form of cacodylate of soda intramuscularly. Particular attention should be paid to the teeth and other foci of infection.

"Based on the studies of Kuhlmann that the erythrolysis in pernicious anemia causes acidosis, Walinski advises the injection, intragluteally, of 5 units of insulin twice daily and later 10 units. During the treatment three blood transfusions of 300 c.c. are given. Under such treatment the alkali reserve in the blood is increased. There is a fall in blood-sugar and the number of erythrocytes in the hemoglobin reach the normal figures."

Aplastic Anemia.—In 1888 Ehrlich²² observed a case of severe anemia in which the normoblasts disappeared from the blood and color index was low. He predicted that there would be rapid fatal termination of this case, as the blood showed that the regenerative power of the bone-marrow had disappeared. He also predicted that the bone-marrow of the long bone would be yellow instead of red because of the absence of regeneration of the bone-marrow. The necropsy proved him to be correct. Ehrlich named this condition aplastic anemia and considered it a terminal stage of some cases of pernicious anemia due to the absolute loss of regenerative power of the bone-marrow. Later observers, such as Eppinger, Sheard,⁹⁰ Schneider,⁸³ and Pappenheim, considered this disease an independent form of anemia. McElroy⁵⁵ defines aplastic anemia as a severe myelopathy with deficient regeneration of the blood elements, characterized in many cases by extreme pallor of the skin, hemorrhages from the mucous membrane, petechiæ and ecchymosis, absence of splenic enlargement, diminished hemoglobin metabolism, absence of plastic changes in the red blood-cells, leukopenia, relative lymphocytosis, and pronounced thrombocytopenia. It is a condition which is

characterized by a serious diminution in the blood-forming function of the bone-marrow. Therefore the red blood-cells, the blood-platelets as well as the leukocytes, are greatly reduced in number. Because of the lack of regeneration of the bone-marrow Pappenheim terms it a "regenerative anemia," and Schneider suggested the term "paralytic anemia." According to Sheard the term "hypoplastic anemia" would be most accurate because it describes best the pathologic findings. This form of anemia is only a pathologic syndrome and may occur secondary to toxic influences causing inhibition of the erythropoietic tissue, or as a result of exhaustion of such tissue due to overstimulation.

Examples of secondary aplastic anemia have been described following severe hemorrhages, severe sepsis, benzol, and trinitrotoluene poisoning, and also secondary to x-ray treatment. Some observers state that the protracted use of arsenic in the treatment of syphilis may give rise to such an anemia. The characteristic features are, low color index, reduced number of red blood-cells. Counts of 600,000 or 800,000 are not infrequent. Leukocytes are likewise diminished considerably, particularly the polymorphonuclears, which vary from 2000 to 2500 and sometimes even less. Poikilocytosis is very marked and the blood-platelets are markedly reduced in number. The serum of the blood is pale, not yellowish. There is, as a rule, very little urobilin in the urine and the indirect bilirubin reaction is negative. Achylia is not present. There is no involvement of the spinal cord and there is no glossitis. The hemorrhagic tendency in this disease, unlike pernicious anemia, is very marked. In fact, the first symptom is bleeding, which is excessive either from the uterus, mouth, or other parts of the body. The disease ends fatally in the majority of cases. Blood transfusions and large doses of iron may have a marked beneficial effect.

"Bailey⁵ reported 2 cases of pernicious anemia with abdominal crisis. They were incorrectly diagnosed—one as perforated gastric ulcer and the other as biliary colic. Both these cases were the result of abdominal crisis which sometimes occurs in the course of pernicious anemia."

CHLOROSIS

Chlorosis is a disease of the female sex usually occurring at the age of puberty. The frequency of chlorosis, according to Cabot, Naegeli, and others, has diminished a great deal. This is most likely due to the fact that the disease was overdiagnosed in previous years, so that many cases of incipient tuberculosis, hyperthyroidism, or even ulcer of the stomach were mistaken for chlorosis. It has been assumed for a long time that chlorosis and ulcer of the stomach are often associated and that chlorosis often leads to ulcer of the stomach. This was likewise an erroneous conception. Based on Virchow's assertion that chlorosis is usually associated with status asthenicus and a narrow aorta, pale looking girls of such status were considered chlorotic, although the characteristic reduction in hemoglobin was not present. This symptom complex was termed "chlorosis larva." According to Naegeli, an individual with status asthenicus is never afflicted with chlorosis. Chlorosis rather effects well-built, muscular girls with a well-developed framework. There is no loss of weight during the disease, but an increase of adipose tissue. The mammae are well developed and often overdeveloped. It has been stated that unhygienic environment, poor food, and bad air are predisposing factors, but this also cannot be confirmed. The disease is rare. It begins at puberty and disappears completely within a few months under proper treatment. There are cases, however, on record where the symptoms recurred in a milder form and sometimes even in a severe form after the age of twenty-five and thirty. On rare occasions the disease may run a chronic course so that women even of middle age show the clinical picture of chlorosis, the degree of the disease varying during different periods of life.

According to von Noorden and Morowitz chlorosis is due either to congenital or acquired weakness of the hematopoietic organs brought about by a dysfunction of the ovary. They explain the etiology of chlorosis in the following manner: In the normal female organism during puberty the monthly loss of a large quantity of blood is quickly replaced by the blood-making organs. In the chlorotic individual this blood-making function

is interfered with by some disturbance in the ovaries. Normally the ovaries secrete a chemical substance influencing the regenerative power of the blood-making organ. Such a substance, according to von Noorden and Morowitz, is missing in the chlorotic individual. Tandler, who is also of the opinion that disturbed ovarian function is a cause of chlorosis, states that the interstitial substance of the ovaries is the seat of disease in chlorosis.

Symptoms.—The appearance of the chlorotic individual is very striking. She appears tired, always very pale, and the sclerae have a greenish hue. The face is puffy and the patient is more tired in the morning than in the evening. The blood-serum is as white as water. If 20 to 30 drops of blood are placed in a capillary tube and allowed to stand in a cool place, the serum separates and the color can be studied.

The gastro-intestinal symptoms are sometimes very striking. There is, as a rule, a complete loss of appetite and often an aversion to food with a perversion in appetite characterized by a craving for sour and spicy foods. Some patients even eat chalk. Gastric secretions are, as a rule, not disturbed and constipation and even obstipation is the rule. Sleep is not disturbed. Naegeli lays special stress on the fact that if a pale girl complains of not being able to sleep chlorosis should be ruled out. Another very striking point which differentiates chlorosis from certain forms of secondary anemia in girls is the fact that amenorrhea is usually present, whereas other forms of blood disturbances in young girls are associated with excessive menstruation.

Blood-picture.—Whereas there is no characteristic blood-picture in chlorosis, it must be emphasized that the oligochromemia is a very striking phenomenon in chlorosis. The hemoglobin is reduced out of proportion to the number of red blood-cells. This may also occur in posthemorrhagic anemia, but never to the same degree. Hemoglobin as low as 50 and even 40 per cent. may be encountered in chlorosis with a red cell count of 4,000,000 and more. In the more severe cases the red blood-cells likewise are reduced to 2,000,000. Marked pallor of the face, marked dyspnea, headache, vertigo and cardiac palpi-

tation, and hemic murmurs are usually present because of the low hemoglobin. The pallor of the stained red cells is most striking. The entire cell looks white with the exception of the border, which is somewhat stained. Anisocytosis is not so common. Microcytes usually predominate. Grosch and Stifel³² have devised a very practical method how to determine the diameter of the red blood-cells. Such a determination is important from the diagnostic standpoint, as in secondary anemia and in chlorosis the diameter of the red blood-cells is usually below normal in contradistinction to pernicious anemia, in which the diameter is above normal. Regenerative phenomena are not infrequently encountered, as indicated by the presence of nucleated red blood-cells in the blood. Macrocytes and polychromatophilia are the great exception. Even after the hemoglobin becomes normal, the subjective symptoms of anemia persist. The blood-platelets are considerably increased, often being as high as 500,000. Matthes calls attention to the fact that thrombosis of the femoral vein is at times a complication of chlorosis because of the increased number of blood-platelets. A more serious complication is thrombosis of the longitudinal sinus, which gives rise to severe headaches and sometimes even cerebral hemorrhage or meningitis. The diagnosis is established if ophthalmoscopic examination reveals dilatation of the roots of the veins which causes swelling of these veins. The swelling is most marked on the parietal parts of the skull, eyebrows, forehead, and occiput. Thrombosis of cavernous sinus may also occur, causing papillary edema, swelling of eyelids, and at times paralysis of the eye muscles. Thrombosis of the transverse sinus with swelling over the region of the mastoid may occur. In these cases there is often thrombosis of the internal jugular vein which may be palpated and which causes pain on movement of the head. In chlorotic thrombosis the spinal fluid is dark yellow. If in the course of chlorosis cerebral symptoms develop, one must think of thrombosis of the longitudinal sinus and perform a lumbar puncture, as this has a favorable therapeutic effect. Matthes also calls attention to the fact that is most characteristic

as the chlorosis improves, polyuria, with diminished specific gravity due to excessive elimination of water, sets in.

Treatment.—This consists of large doses of iron, preferably in the form of reduced iron, 0.3 to 0.6 gr. three times a day. The inorganic iron is as effectual and even more so than the organic iron. This was again proved by the studies of Seyderhelm.⁸⁸ Scott⁸⁶ furnished most valuable experiments and demonstrated conclusively that the inorganic iron is well absorbed. He fed 9 rats, eight weeks old, exclusively on bread and milk in order to produce severe anemia. He then added to the diet of one group of animals 20 mg. of iron chlorid every day. After sixteen weeks the hemoglobin in the animals fed with iron was as high as 95 per cent. and the red blood-cells were normal. The animals who did not receive the iron remained with a hemoglobin of only 55 per cent. Notwithstanding the fact that the theory of ovarian internal secretion disturbance is so plausible, the therapeutic use of ovarian extract did not prove satisfactory. In addition to the above treatment, nourishing food, fresh air, etc., are essential.

RARE FORMS OF ANEMIA

Moschcowitz described an acute febrile pleiochromic anemia with hyaline thrombosis of the internal arteries and capillaries. Previous to this Brill,¹⁰ MacIntosh, and Cleland⁵⁷ described similar conditions. In Brill's case transfusion brought about a cure. Lederer⁵⁰ described 3 cases of acute severe anemia with alterations in the blood similar to those seen in pernicious anemia. All 3 cases recovered promptly after single transfusion. They were all characterized by sudden onset, fever, and marked leukocytosis. The number of normoblasts were enormous. In one instance it amounted to 3000 c.mm.

Severe anemia occurs in the course of agranulocytic angina, which was described in 1922 by Schultz and Versè,⁸⁵ and later by Friedeman.²⁶ In the American literature there are excellent contributions by Kiles and Piette. The disease sets in acutely, with high temperature, necrosis of the mucous membrane of the mouth, pharynx, tonsils, and a marked reduction, and often a complete absence of neutrophilic leukocytes. Piette studied the

histopathology of a case and found that the structure of the spleen was markedly changed and that there was enormous development of the sinus endothelial system at the expense of the lymphatic tissue. In some of the capillaries bacterial emboli were encountered. The most pronounced changes were in the kidneys. Innumerable bacterial emboli were distributed over the cortex, and were particularly abundant in the region of the vas afferens and in the glomeruli. The suprarenal glands likewise contained numerous emboli in the capsule of the cortical substance without any evidence of inflammation. Piette asserts that the disease is of bacillary origin and it is probably due to *Bacillus pyocyaneus*.

Anemias occurring in children are of special interest and will be briefly discussed. These anemias are associated with a large spleen. They have been designated under various names, such as splenic anemia, rachitic anemia, or anemia pseudoleukemia infantum (von Jaksch). Kleinschmidt, in the clinic of Czerney, gives the interpretation of the etiology of anemia in childhood. This author experimented on animals and found that the withdrawal of iron in the diet may bring about marked anemia which can be made to disappear by the administration of inorganic or organic iron. It therefore appeared to him that the anemia in childhood is the result of exclusive milk diet because it is poor in iron. In that form of anemia where there is no enlargement of the spleen and where the blood-picture is that of chloranemia, the assertion of Kleinschmidt has been fully confirmed. He describes the following characteristics for this form of anemia: It occurs almost exclusively in constitutionally weak children of a neuropathic or exudative diathesis type and also in rickety children. There is a marked reduction in hemoglobin. The number of leukocytes is normal. The lymphocytes predominate. He named the disease "alimentary anemia." Czerney does not believe that the anemia is necessarily due to lack of iron, but he is of the opinion that it is the result of one-sided diet. It is rather striking that in the fatal forms the bone-marrow is found to be bluish red and there is hemosiderosis of the liver as a sign of increased blood destruction.

A frequent cause for anemia in children is lues. This occurs earlier in life than alimentary anemia and is accompanied by a large liver and spleen. Other forms of anemia which occur as a result of tuberculous adenitis and Barlow's disease are symptomatic anemias without any special characteristics.

Thrombopenia.—Thus far anemias were described in which there is a primary disturbance in the erythropoietic system. A brief description will be given of the anemias occurring as a result of a disturbance in the megacaryocyte.

The various forms of purpura hemorrhagica belong to this group. In 1740 Werlhoff described a symptom complex which he named morbus maculosus hemorrhagica, which has been known since then as Werlhoff's disease. It is recognized hematologically by a marked reduction in the blood-platelets, hence Frank applied the name "thrombopenia" and Eppinger named the disease "thrombocytopenia." The mother-cell of the thrombocyte, namely, the megacaryocyte, is most likely the primary seat of the affection, producing blood-platelets of an inferior quality which are readily destroyed by the spleen (Brill,¹⁰ Rosenthal, Held³⁵). This explains the reason why the symptoms disappear after splenectomy, although a short time after the operation the blood-platelets are again greatly reduced. After the seat of destruction of blood-platelets, namely, the spleen, is removed a smaller number of blood-platelets even of an inferior quality suffice to remove the tendency to hemorrhagic diathesis. In the benign form of thrombopenia changes in the blood are not very marked, with the exception that during the height of the disease the blood shows signs of moderately severe secondary anemia of the chloranemic type. The shape of the red blood-cells is only moderately altered, but the microcytes predominate. Even in the milder cases there is, as a rule, a moderate reduction in the number of leukocytes at the expense of the polymorphonuclear cells. In the very severe forms (the malignant type of Frank) the blood changes are very marked. The blood-platelets may be reduced to 10,000 or even lower. Anisocytosis and poikilocytosis are marked and the microcytes are very numerous. Signs of blood regeneration indicated by the presence of nucleated

red cells are rarely encountered. Most striking in the malignant form is the marked reduction in the number of white cells, particularly the polymorphonuclear cells. Counts of 2000 or less are not infrequent, of which 80 to 90 per cent. may be monocytes. Abnormal white cells are not very infrequent, although myelocytes are occasionally present. From this blood-picture it is evident that although the megacaryocytes are primarily affected, the erythropoietic and leukoblastic elements are likewise involved in the malignant cases unless quickly checked by the proper therapeutic measure, namely, the removal of the spleen, which was first advocated by Kaznelson.

Clinically, the milder type is characterized by petechiae scattered all over the body and mild hemorrhages from the mucous membrane of the mouth, pharynx, and nose. At times excessive menstruation may be the only evidence of the disease. The benign form has a tendency to recur, but the prognosis is good.

Another type which is somewhat severe was described by Henoch and is known as Henoch's purpura. It begins with abdominal pain which is sometimes localized over the appendicular region simulating appendicitis. There is, as a rule, no abdominal rigidity. These pains are soon followed by bloody evacuations which clears the diagnosis.

Another type of the disease which runs a mild course and which has a tendency to recur was first described by Schönlein, which he names "purpura rheumatica poliosus." The purpuric spots are most marked around the joints, arms, and legs. Ottenberg rightfully states that the disease should not be named rheumatic purpura, because it has nothing in common with rheumatism. It never leads to endo-peri-pancarditis, the joint pains are not very severe, acid sweats are absent, and salicylates have no favorable effect.

The most malignant type is the so-called "essential thrombopenia" (Frank) in which the hemorrhages are not very severe. Hemorrhages occur not only from the mucous membrane of the mouth, nose, uterus, and rectum, but also into the pleura, pericardium, and brain. The anemia is extreme in such cases.

The diagnostic feature in all forms of thrombocytopenia are: Marked prolongation of bleeding time which according to Duke's method is determined in the following way: The lobe of the ear is punctured and the blood is allowed to flow. Normally it oozes from one to three minutes. In thrombopenia it is prolonged as long as ten minutes and even for hours.

A second important sign is the one by Hayem, namely, the failure of the blood-clot to retract. Brill and Rosenthal pointed out that in thrombopenia before splenectomy, even if the thrombocytes are increased to 80,000, the clot fails to retract. The coagulation time is not interfered with. Another important diagnostic sign is the capillary resistance test (Rumpel-Leede, Hess). This sign depends on the diminution of thrombocytes and the associated pathologic condition of the capillaries. A tourniquet is applied to the arm from one to four minutes, tight enough to prevent the return circulation without obliterating the pulse. Depending on the degree of hemorrhagic diathesis, petechiae, or even large ecchymotic areas, appear on the forearm.

It is of great importance to be familiar with this form of thrombopenia because splenectomy is a life-saving procedure. Blood transfusion, on the other hand, has hardly any beneficial effect, and it seems to me that it is even harmful because of the damaged capillaries.

In the milder forms symptomatic treatment usually suffices. This consists of the administration of 5 to 10 drops of Fowler's solution three times a day; calcium lactate 15 gr. three times a day, or Ringer's solution by hypodermoclysis three or four times a week. Severe bleeding is controlled sometimes by the intramuscular use of serum of thromboplastin (Hess) or other foreign proteins, and at times also by the intravenous administration of 10 c.c. of 5 per cent. calcium chlorid or 5 c.c. of a concentrated sodium chlorid solution. In some cases x-ray treatment over the spleen may stop the bleeding.

Malignant essential thrombopenia must be differentiated from aplastic anemia, the characteristics of which were described above. In the latter disease splenectomy is contra-

indicated. Malignant essential thrombopenia must be differentiated from aleukia or aleukemic leukemia. In this affection there are also hemorrhages from the mucous membranes, but the blood-platelets are never reduced to the same degree, and although the white cells are so markedly diminished, those present are of a pathologic character consisting mainly of pathologic lymphocytes and myelocytes. There is also evidence of regeneration of the bone-marrow in this affection which is indicated by the presence of normoblasts, Howell-Jolly bodies, and Cabot's rings. The spleen in thrombopenia if enlarged is only slightly so, whereas in aleukemia the spleen is considerably enlarged.

Severe streptococcic sepsis is sometimes mistaken for thrombocytopenia or aleukia. Streptococcic sepsis is accompanied by marked hemorrhagic diathesis. Although in these cases there may be a leukopenia, the polymorphonuclear cells are present to the extent of 50 to 60 per cent. This is never the case in thrombocytopenia or aleukia.

Another affection which deserves mention is endotheliosis hemorrhagica (Morbus, Litten). This was first observed by Litten in association with bacterial endocarditis. It is characterized by the presence of macrophages in the blood which possess a phagocytic property. There is a decrease in the number of neutrophils and a relative increase in lymphocytes. It seems that in this affection the defense against the *Streptococcus viridans* is characterized by the absence of a myelocytic element which normally causes an increase in the neutrophilic leukocytes. Kuczinsky and Wolf showed that the defense is the work of the endothelial elements in the spleen and kidney. Libman is inclined to ascribe great importance to the macrophages in the process of immunity. The disturbance in the endothelial elements explains the hemorrhagic tendency in bacterial endocarditis which is characterized by petechiæ and even bleeding from the mucous membrane of the internal organs. Thrombocytes are only moderately reduced, hence the bleeding time is normal. The capillary stasis test, on the other hand, is positive.

Scurvy.—Another condition, which belongs to the group of hemorrhagic diathesis and which often gives rise to secondary

anemia, is scurvy. In the majority of cases it is recognized by the bleeding from the gums. It must be emphasized, however, that quite frequently there is no bleeding from the gums during the early stage of the disease, at which time treatment is most effectual. It is also important to remember that the bleeding from the gums occurs only in places where there are no teeth. In severe cases the hemorrhages extend into the muscles, especially the muscles of the calf. Hemorrhages into the joints and even into the peritoneum and pleura may occur. In neglected cases abscesses form in the bleeding areas which result in fatal sepsis. Selle and Rosenberg⁸⁷ pointed out that bleeding in the muscles of the calf is particularly frequent in adults and that these patients have a tendency to walk on the tips of the toes. They also state that there are trophic disturbances of the skin and the hemorrhages have a tendency to appear exclusively in the region of the hair-follicles. The blood-picture is that of secondary anemia the severity of which depends on the degree of hemorrhages.

Hemophilia, which is, as is well known, encountered exclusively in the male sex, often leads to severe secondary anemia. This disease begins early in childhood and lasts for a number of years. The disease has a tendency to become milder and even disappear in those who live to maturity. Male children are affected through maternal heredity. Although women are not affected, I know of a woman of hemophilic stock who bleeds profusely during her menstrual periods and has unexplained hemorrhages from the rectum. Her coagulation time is markedly prolonged. Infants are usually free from the disease, although in some cases the cutting of the cord and circumcision may cause fatal hemorrhage because of the inborn hemophilic tendency. Bleeding may occur from almost any area, but hemorrhages from the gums, throat, and nose are most frequent. In severe cases hemorrhages from the stomach, kidney, and rectum may be present. Hemorrhages into the joints or hemarthrosis occur sometimes which simulate arthritis. The skin hemorrhages in hemophilia, in contradistinction to purpura, are usually the result of trauma which may be so slight that the patient believes the hemorrhage

was spontaneous. The hemophilic tendency is first disclosed when the patient undergoes a minor operation, such as extraction of a tooth, or when he cuts himself accidentally. The fatal hemorrhage after tonsillectomy is usually the result of hemophilia. In male individuals before the age of thirty it should be compulsory to test the coagulation time before any operation, especially before tonsillectomy, is performed. As to the blood findings, the prolonged coagulation time is very important. The blood-platelets are, as a rule, not markedly reduced. Even in mild cases the blood shows moderate changes of secondary anemia. In severe cases marked microcytosis, poikilocytosis, and anisocytosis may be present.

Hereditary Hemorrhagic Telangiectasia.—This is characterized by a dilatation of the superficial venules and capillaries of the skin of the mucous membranes which have a tendency to spontaneous hemorrhage. Sometimes severe hemoptysis may be the result of such familial telangiectasia. Libman and Ottenberg observed persistent hemoptysis of several members of one family which they called "familial hemoptysis" and which is most likely due to hereditary telangiectasia. If the bleeding is marked secondary anemia results.

LEUKEMIA

Acute Leukemia.—Just as in anemias, there is eventually involvement of the leukoblastic and megacaryocytic elements causing the appearance of abnormal white cells in the blood and disturbance in blood-platelets leading to hemorrhagic diathesis, so, in leukemia, changes result in the erythropoietic system leading to anemia. Whereas an outspoken case of lymphoid or myeloid leukemia is easily recognized by the clinical picture and by the examination of the blood, atypical cases are present which often offer great difficulties in diagnosis.

Acute lymphatic leukemia runs a course closely resembling sepsis. In the midst of perfect health or, at most, preceded by a short period of malaise, weakness, moderate elevation of temperature, bleeding from the gums, or toothache which brings the patient to the dentist, who extracts one or more teeth, the

patient suddenly develops severe ulcerative tonsillitis, stomatitis, and gingivitis. There is oozing or free bleeding from the affected area and frequently also bleeding from the nose. The tonsillar affection is so severe as to simulate streptococcic tonsillitis, Vincent's angina, or diphtheria. These cases are often treated for Vincent's angina or diphtheria for many days because of failure to examine the blood. In hospitals, where the blood examination is a routine procedure, such a mistake is impossible. Further evidence of hemorrhagic diathesis manifests itself by petechiæ scattered all over the body. The temperature is elevated, sometimes as high as 105° F. The sensorium is dull; patient is apathetic, low muttering delirium is, as a rule, present. Almost all the superficial glands are enlarged. The glands are small and not tender. The spleen is considerably enlarged. The blood shows a marked increase in white cells, as much as 120,000 to 150,000 and at times more, of which 80 to 90 per cent. are lymphocytes. There is a marked reduction in hemoglobin. Microcytosis and vacuolization of the red blood-cells are present. The disease usually terminates fatally within a few days or, at most, in a week.

Another form of acute leukemia which clinically closely resembles lymphatic leukemia is the acute myeloblastic leukemia. The nucleus of the white cell resembles the myelocyte, but its protoplasm is not granular. This white cell Naegeli terms "myeloblast." It very often resembles a large lymphocyte. It differs from the latter by the positive Winkler-Schulze oxydase reaction. This form of leukemia is likewise fatal, but runs a longer course. Both these forms occur more frequently in children, but they may also occur in adults. The cause is entirely unknown and the treatment is not effectual. Transfusion of blood is, as a rule, employed. Calcium intravenously has been advocated. From the practical standpoint only symptomatic treatment can be advocated, which consists of treating the mouth with mild antiseptic lotions, the administration of 10 to 20 per cent. glucose solution rectally by the Murphy drip method, and large quantities of fluid by mouth. The elevation of temperature is to be controlled by hydrotherapeutic measures.

Differential Diagnosis.—At times acute leukemia of myeloblastic or lymphatic type may run a course without an increase in leukocytes. At times there is even a marked decrease (sub-leukemia or aleukemic type of leukemia). Under such conditions the disease may be mistaken for severe sepsis, aplastic anemia, or agranulocytic angina. Leukemia is differentiated from sepsis by the fact that in the latter ulceration of the throat, nose, and gums is never marked. There may be a mild stomatitis, but never severe ulceration such as is encountered in acute leukemia. In severe sepsis the micro-organism can, as a rule, be isolated from the blood. Petechiæ and other manifestations of hemorrhagic diathesis are not so marked in sepsis. On the other hand, chills and remittent type of temperature are the rule. The blood always shows a large number of polymorphonuclear leukocytes. The staff-shaped cells (stabkornige) are present in large numbers. Immature white cells (myelocytes) are likewise encountered. The superficial lymph-glands in sepsis, if enlarged, are usually in the region where the septic focus is most marked, as, for instance, in the neck in case of streptococcic sore throat.

In aplastic anemia no glandular enlargement is noted. Bleeding from the nose, uterus, and rectum precedes the acute symptoms. The temperature is not very high and the anemia much more severe than in leukemia. The hemoglobin is about 15 per cent. and a red count of 600,000 is not infrequent. Microcytosis, Howell-Jolly bodies, and Cabot's rings are present.

Agranulocytic angina likewise fails to show enlargement of the superficial glands. Petechiæ are also not very marked, whereas reduction in white cells is very marked.

There is another disease from which acute leukemia must be differentiated, and that is the acute benign lympho-adenosis (Longcope), also known as glandular fever. Although this disease occurs more frequently in children, it is also encountered in adults. The most striking features are the enlargement of the superficial glands, enlargement of the spleen, and elevation of temperature. Sore throat is usually present, but no severe ulceration. Petechiæ are not present. There are no other signs

of hemorrhagic diathesis. The blood shows a marked increase in lymphocytes. The disease terminates favorably.

Chronic leukemia may occur either in the lymphatic or myelogenous types. The lymphatic type is characterized by enlargement of most of the superficial glands, and of the spleen, pallor, extreme weakness, moderate and transient rises in temperature, and hematologically, by a marked increase in white cells, of which 80 to 90 per cent. are lymphocytes. The large lymphocytes usually predominate and often lymphocytes with indented borders (so-called Reider cell) are present. This disease runs a chronic course, lasting sometimes three to five years, and is favorably influenced by x-ray or radium treatment and large doses of arsenic. During the remission all the symptoms and signs may disappear. During the active stage of this disease a marked degree of secondary anemia is present. The outspoken clinical picture just described offers no difficulty in diagnosis, but cases are encountered where the increase in leukocytes is not so marked. The enlargement of the glands is confined to isolated areas. Cases are reported where the enlargement of one parotid gland was present. At times only salivary and lacrimal glands are enlarged simulating Mikulicz's disease. In these cases only a very careful examination of the blood will disclose the true nature of the disease. In those cases where there are only a few isolated glands they may be mistaken for tuberculous or syphilitic glands. In some cases biopsy must be resorted to in order to establish a diagnosis. The enlarged tuberculous glands always coalesce. They are tender to touch, the underlying skin is adherent, and suppuration occurs frequently. Luetic glands also coalesce and are usually much larger than those found in cases of lymphatic leukemia. They have a tendency to suppurate in the inguinal region. The spleen is never enlarged in luetic or tuberculous adenitis as it is in chronic lymphatic leukemia.

Myelogenous Leukemia.—The main characteristic feature in myelogenous leukemia is the enormous enlargement of the spleen. Next to splenomegaly of the Gaucher type, the largest spleen is encountered in this form of anemia. There are cases in which there is only moderate enlargement of the spleen. The splenic en-

largement often causes discomfort in the left hypochondrium and sometimes even severe pain. It may sometimes push up the left dome of the diaphragm, causing atelectasis of the left lower lobe simulating left pleural effusion. There is usually tenderness over the long bones and sometimes even over the sternum. Weakness and loss of appetite are very marked. Very often there is nausea and vomiting. The hematologic examination clears the diagnosis. There is a marked increase in the leukocytes (100,000), consisting almost exclusively of myelocytes. The myelocytes consist chiefly of polymorphonuclears and basophilic cells and some eosinophils. Cases are reported in which the eosinophilic type predominates (Bass and Shapiro).

Plasma-cell Leukemia.—A rare form of leukemia worthy of mention is plasma-cell leukemia. This is characterized by localized tumors which consist almost exclusively of plasma-cells, and therefore also known as plasmoma or plasmacytoma. Such tumors have been encountered in the cornea as well as in the pleura and other locations. Generalized plasma-cell hyperplasia of the lymphatic apparatus with and without the blood-picture of leukemia may occur. Gluzinski and Reichenstein, quoted by Hirschfeld, described a case in which, in addition to the multiple plasma-cell myeloma, the spleen and all the superficial glands were enlarged. There was a marked reduction in the number of red blood-cells and the white cells were increased as high as 40,000 with 91 per cent. lymphocytes in which the plasma cells were very numerous. According to Hirschfeld there seems to be a transition between lymphatic leukemia and plasma-cell leukemia.

Chloroma.—Another rare form which is sometimes classified with leukemia is chloroma which, because of its resemblance to leukemia, is also known as chlorleukemia. Allan-Burns² was the first to observe a patient in whom exophthalmus, tumor of the eyeball, and blindness resulted. The removal of the tumor showed the lacrimal glands to be greenish in color. In 1853 King named the disease "chloroma," and in 1858 Recklinghausen called attention to the fact that the disease is closely allied to leukemia.

The general symptoms consist mainly of marked weakness, loss of appetite, and occasional elevation of temperature on slight

exertion. The tumor masses is the main feature of the disease. They may be localized in any part of the body, but are most commonly found in the bones of the skull. There is a case mentioned in literature where the tumor was found in the mammary gland. At times it may also be situated in the thorax or in the abdomen causing pressure symptoms, the exact cause of which cannot be determined during life. Branwell described a case where the follicles at the root of the tongue were involved and where the green color of the tumor could be distinguished even during life. Ordinarily the greenish color of the tumor can only be seen after excision. At times the tumor is situated in the orbit of the eyeball, causing marked exophthalmos. It may invade the labyrinth, causing Ménière's symptom complex. It may also invade the hard palate or the nasal cavity. The tumor may cause facial paralysis. At times the thyroid may be the primary seat of the disease. Cases are on record where the tumor invaded the pancreas, giving rise to glycosuria. Occasionally it may invade the spinal cord, causing compression myelitis. If the bone-marrow is the main seat of the disease, it may simulate multiple myelomata, causing the appearance of Bence-Jones bodies in the urine. These bodies are detected on heating the urine to 40° to 60° F.; cloudiness results, which disappears on further heating.

The blood-picture may be sometimes only of secondary anemia. In most cases, however, a leukemic blood-picture either of the lymphoid or myeloid type may be present. Some authors state that what is considered the lymphoid type is, in reality, a myeloblastic type. The number of leukocytes may vary. There are cases on record where the leukocytes are as high as 100,000 and even 200,000. This disease occurs more frequently in children and terminates fatally within one to one and a half years.

HODGKIN'S DISEASE (LYMPHOGRANULOMA. LYMPHO-BLASTOMA). (MINOT, ISAACS.)

Up to the time when Paltauf and Sternberg described the exact clinical and pathologic picture of Hodgkin's disease the differentiation between this form of adenopathy, lymphosar-

coma, and luetic and tuberculous adenopathy was very indefinite. Virchow separated pathologically lymphogranuloma from sarcoma of the lymphatic glands. Hodgkin's disease is much more frequent in men than in women. It occurs usually between the ages of twenty and fifty. It runs a chronic, progressive course, eventually terminating fatally. The average duration is about two to three years, although cases have been reported which lasted much longer. The case of Stockman lasted twenty years. Reed described a case which lasted seven and a half years. There are cases, however, which run a very acute course. I saw a case through the courtesy of Dr. Louis Greenwald which lasted only three months. It is quite difficult, as rightfully pointed out by Green, to judge the duration of the disease, because the patient often presents himself for examination when the disease is quite advanced, or when the glands of the neck are very large. It is well known today, however, that the glands in the neck are most often the result of affected glands in the mediastinum. There is a case on record where one gland was found in the bronchus in a patient who died of an intercurrent disease. In a case of this kind the other glands might have become enlarged later, and it would have been impossible to foretell where the disease began. Symmers, in his excellent contribution, showed that the glands may be found in the most unusual locations and that cases are encountered where the spleen may be the primary seat of disease.

The true causative factor is practically unknown, although mention must be made of the work of Bunting and Yates.¹² These authors isolated and cultured a Gram-positive diphtheroid bacillus which they named "*Corynebacterium granulomatis maligni*." This bacillus when grown in pure culture and injected into apes produced an enlargement of glands and histologic changes similar to, if not identical with, those of Hodgkin's disease. Fraenkel and Much reported Gram-positive granular non-acid-fast bacilli, considered by some degenerated tubercle bacilli. It may be stated, however, that but little evidence can be offered which would support the assertion of Sternberg that the disease is of tuberculous origin. The studies of

Arkin⁴ indicates that the disease often occurs in several members of the same family. He described the so-called familial mediastinal lymphogranuloma.

The main feature of the disease is the enlargement of the lymphatic glands. This often begins in localized areas, especially in the cervical region. Sometimes the first enlarged glands may be noticed in the axillary region and less frequently in the inguinal region. It must be emphasized that not infrequently the glands of the mediastinum and retroperitoneal region, as well as those of the gastro-intestinal tract and lungs, may be affected. The superficial glands may be only moderately affected. At times one or two small isolated glands may be found in the cervical region on the involved mediastinal side. At times the spinal cord may be involved, giving rise to paralysis masking the true nature of the disease. Glands in the chest may grow very rapidly causing marked pressure on the adjacent organs. As a rule, however, these grow very slowly, and notwithstanding the fact that the Roentgen examination may reveal large tumors invading the mediastinum, the pressure symptoms are comparatively mild. This is due to the extreme slow growth of the glands with subsequent accommodation of the thoracic viscera. The spleen is considerably enlarged and the liver only moderately so. The enlarged superficial glands are usually hard, but the overlying skin is freely movable. They are, as a rule, not tender and maintain their outline until late in the disease. If, as is usually the case late in the disease, periadenitis occurs, the tumors may become lobulated. On very rare occasions the glands soften and suppurate. In cases where the superficial glands are enlarged the diagnosis is, as a rule, not very difficult. As the diagnosis often depends on the histologic picture, brief mention of the description of the same must be made. The granulomata do not consist exclusively of lymphocytes, as is the case in lymphatic leukemia, but consist of inflammatory granulation with a variety of cells which reminds one of tubercles. The typical histologic picture described by Reed,⁷⁹ namely, the swollen endothelial cells lying upon the fibrils or reticulum, the large epithelioid giant-cells (Sternberg⁸⁰), lymphocytes, and eosinophils occupying

the interstices of the stroma, will clear the diagnosis. If only the mediastinal or retroperitoneal glands are involved the diagnosis is very difficult. In these cases, however, the associated enlargement of the spleen will help in the differential diagnosis.

In lymphosarcoma (Kundrat's disease) the mediastinal and retroperitoneal glands are much more frequently enlarged than the superficial glands, although the axillary, inguinal, and cervical glands are often likewise enlarged. The spleen is hardly ever enlarged, and if so, only to a moderate degree. The mediastinal glands grow so rapidly that the most severe pressure symptoms in the thorax are produced. Furthermore, in lymphosarcoma the lymph-follicles of the gastro-intestinal tract are often enlarged, giving rise to marked gastro-intestinal symptoms and often hemorrhages from the gastro-intestinal tract. Sometimes the hemorrhage from the gastro-intestinal tract may be the only symptom. I remember a case in which the hemorrhage from the stomach was so marked that a diagnosis of ulcer of the stomach was made and operation was performed. Elevation of temperature which occurs frequently in lymphogranuloma is very rarely present in lymphosarcoma. In doubtful cases the x-ray or radium treatment will decide whether lymphosarcoma or lymphogranuloma exists. The former yields much more rapidly to x-ray treatment. If lymphosarcoma is suspected, the biopsy is a dangerous procedure because it brings about rapid spread of the disease. It is, therefore, more advisable to resort to x-ray or radium treatment as a differential diagnostic method.

A symptom that is usually in favor of lymphogranuloma is itching of the skin. This may precede the enlargement of the glands by a number of months. Lymphogranuloma does not affect constitutionally inferior individuals; it affects more the robust type and not those of the status thymicolymphatic type. This is the reason why patients with lymphogranuloma seldom show involvement of the tonsils or peritonsillar tissue; whereas those with lymphosarcoma show marked involvement of the tonsils, sometimes even ulceration. Furthermore, in lymphogranuloma there are very frequent rises of temperature. The temperature curve which was first described by Pel and by Eb-

stein is usually of a remittent type and may last for weeks, simulating sepsis. At times the temperature may be of a continuous type, simulating typhoid fever. During the rise in temperature the glands as well as the spleen become more enlarged. The spleen, which is subject to infarcts in this disease, may become so large as to cause pain. In the advanced cases enlarged mediastinal glands often give rise to pleural effusion and those in the abdomen give rise to marked ascites. Pressure on the inferior vena cava may also give rise to edema of the lower extremities as well.

The external appearance of the patient, if the glands of both sides of the neck are enlarged, is quite characteristic. The blood-picture is that of secondary anemia or chloranemia. If marked mediastinal involvement causes cyanosis, symptomatic polycythemia may result. In most cases there is a moderate leukocytosis, but in some, and particularly during the febrile stage, the leukocytosis may be very marked (50,000 or more). Bunting reported a case in which there was 100,000 leukocytes. The polymorphonuclear cells predominate particularly during the febrile stage. During the afebrile stage large and transitional mononuclear leukocytes may be present. The lymphocytes are usually diminished in number, and in the later stage of the disease they may be as low as 10 or 15 per cent. The urine gives a positive diazo reaction and often contains urobilin.

In the differential diagnosis one must also consider tuberculous lymphadenitis. As a rule the differential diagnosis is not very difficult. Tuberculous lymphadenitis occurs in young individuals, affecting chiefly the glands of the neck. The affected glands usually coalesce, become attached to the overlying skin, and are tender to touch. They have a great tendency to suppurate, leading to so-called scrofulosa. There are, however, cases in which generalized tuberculous lymphadenitis is present affecting almost all the superficial glands. The bronchial glands are also enlarged and there is even moderate enlargement of the spleen. The roentgenologic appearance of the glands in the chest often suffices to differentiate tuberculous glands from lymphogranuloma, the former being confined more to the hili. These

tuberculous glands are denser because of the excess of calcium. They are irregular in outline and of varying sizes. Some are as small as a small hazelnut, and others the size of a large plum. The posterior mediastinal space is, as a rule, entirely free from glands. In doubtful cases the histologic examination of the excised gland will clear the diagnosis.

Mention must be made of luetic lymphadenitis. The enlargement of the glands in the secondary lues, whether other manifestations of lues are present or not, offers no difficulty in diagnosis. There are cases, however, in which there is a general lymphadenitis with enlargement of the spleen and secondary anemia in the tertiary stage of syphilis. Biopsy must be resorted to in such cases in order to establish a positive diagnosis.

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THE CLINICAL SIGNIFICANCE OF ANHEMOLYTIC STREPTOCOCCI (VIRIDANS) IN THE BLOOD- STREAM

THE occurrence or absence of anhemolytic streptococci in the blood-stream have important bearing in many conditions. Thus, it is recognized that such a streptococcemia can often accompany an infection of the heart valves, resulting in the well-defined clinical picture, bacterial endocarditis. But it is not so well appreciated that bacterial endocarditis exists with constantly negative blood-cultures or that an anhemolytic streptococcemia can arise in conditions such as focal infections, or as transient and preagonal blood invasions.

The purpose of this discussion is to indicate the clinical significance of anhemolytic streptococci when they are present or absent in the circulating blood.

I. BACTERIAL ENDOCARDITIS

The presence of anhemolytic streptococci in the blood usually means an infection of the endocardium. These organisms are seldom found in acute bacterial endocarditis, but in the subacute and chronic forms they occur frequently. There are, however, indisputable instances of subacute bacterial endocarditis when clinical observations alone are adequate for the diagnosis, and where repeated failure to find streptococci does not weaken the authenticity of this diagnosis. There are also special circumstances when sterility of the blood is the rule; and this sterility is not to be construed as a haphazard happening nor as proof of

the absence of subacute bacterial endocarditis. The commonest form of bacterial endocarditis is:

A. Subacute Bacterial Endocarditis.¹—This malady begins insidiously; indeed, in the beginning patients often refuse to believe that they are sick, the symptomology being so mild and slow moving in its evolution. The earliest complaints reflect a low-grade infection-fatigue, weariness, general malaise, leg pains, anorexia, disturbances of the heart. Even when and as the condition grows sharper and clearer in its clinical outlines its true nature frequently is unrecognized; instead, incipient pulmonary tuberculosis or mild typhoid or malarial fever or rheumatism or general sepsis is misguidedly suspected. Fever arises soon, continuous or intermittent, lasting to the lethal end or vanishing for a few weeks before exitus, as in cases with renal insufficiency. In addition, there are chills, marked sweating, prostration, anemia secondary in character with a polynucleosis or an accompanying leukopenia and relative lymphocytosis, as well as embolic phenomena. Some students have charted two chief phases in this disease—an early stage, the low-grade infection period already noted, and a later stage during which embolic manifestations are prominent. So sharp a demarcation, however, is not tenable; the disease assumes too rich a variety of possible patterns and signs and symptoms. Nevertheless, features referable to embolic localizations are frequent and almost pathognomonic. Thus, we encounter non-elevated petechiæ (some can be white-centered) arising in wave-like crops or showers upon the skin, mucous membranes, especially of the conjunctiva or in the fundi of the eyes; they may specially appear as one or few isolated almost unperceived lonely lesions in the conjunctiva, along the cervical lateral triangles, or between the webs of fingers or toes. There are also hemorrhagic lesions; these are very characteristic of subacute bacterial endocarditis. So, too, are the Osler nodes, to be distinguished from so-called "Janeway lesions²;"

¹ The clinical understanding of this disease has been greatly enriched by the bedside observations of E. Libman. In the description used here much of his work has been incorporated.

² So named and clinically stressed by E. Libman.

the former along the tendons of the fingers and toes, seen in sub-acute bacterial endocarditis, consist of tender, cutaneous nodes which leave a residual spot of brownish pigmentation as they fade, while the "Janeway lesions" on the palms and soles are met almost exclusively in acute bacterial endocarditis and have no left-over pigment area. Clubbing of the fingers may be present, the fingers are pale and not cyanotic as in congenital cardiacs. The clubbing phenomena may exist before bacterial endocarditis occurs. Bone tenderness is often elicited (over the lower end of the sternum, at the epiphyseal junction line, over the anterior surface of the tibiae), and there is a peculiar "café au lait" facial coloration (especially in protracted cases when the blood becomes sterile). The spleen enlarges, sometimes with infarction and acute perisplenitis, and gastro-intestinal, cerebral, ocular fundi, and heart disturbances can follow. Hematuria is an important finding and points to kidney involvement. The cardiac findings can remain relatively insignificant; often a heart defect is unknown to the patient, so little is this organ apt to contribute any part to the symptomatology of this condition.

From the very start there may be an early or fleeting bacteremia, or bacteria in the blood can persist throughout the entire course of the disease. *In over 90 per cent. of cases, during the active stage, anhemolytic streptococci have been recovered.*¹ As a

¹ The references below are on subacute bacterial endocarditis. Many of these publications assert that this disease is caused by anhemolytic streptococci:

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corollary it might, therefore, be adduced that these organisms in the circulating blood-stream, in the great majority of cases, denote a subacute infection of the endocardium, and yet, more than this, positive blood-culture and cardiac valve alteration are required to establish a diagnosis of subacute bacterial endocarditis. The clinical evidences outlined above must be present in full or at least convincing measures, especially features such as white-centered petechiæ. Osler's nodes, emboli, or large spleen with fever and unyielding anemia.

Success in capturing bacteria from the blood depends, to a considerable degree, upon the care and skill with which blood-culture technic is undertaken. To begin with, samples of blood should be drawn at varying intervals of time within a twenty-four-hour period. On occasions it is expedient to try culturing the blood as the patient develops fresh scattered crops of petechiæ or embolization into a tissue or organ concomitant with a chill or with the highest peak of fever.¹ All technical details deserve

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¹ On the other hand, Libman states "that in some cases with high temperatures with very marked oscillations one fails, at times, to obtain bacteria in the blood-culture, although bacteria are present in enormous numbers in the vegetations in the heart"—while in the bacterial stage of the disease, when the temperature is not high, bacteria are nearly always secured (*Amer. Jour. Med. Sci.*, November 13, 1913, p. 634).

the nicest and greatest attention. There are times when only an anaërobic culture method makes possible a positive blood-culture and once in a while media, especially devised and enriched with tissues, are useful.¹

The disease with its constant or recurrent anhemolytic bacteremia may last four to eighteen months; sometimes over two years, but this is not usual. Exitus arrives with severe heart insufficiency (partly produced by the frequently present antecedent rheumatic alteration of lining, valves, and muscles), or from extreme exhaustion associated with intense anemia. A uremic end is not unlikely in patients who have contracted a diffuse (embolic) glomerular nephritis,² that is to say, in those patients with well-developed clinical manifestations whose blood has become bacteria free.

Accordingly, in authentic cases of subacute bacterial endocarditis the clinical picture can continue unabated while the blood is nearly always laden with anhemolytic streptococci or else the blood-culture is positive sporadically or not at all. Verrucae from the heart of these cases contain bacteria plentifully.

The Bacteria-free Stage.—For some unaccountable reason the blood during the active stage of this disease may become sterile. Failure to recover bacteria from the blood-stream does

¹ For a recent discussion on the bacteriology and methods of culture see Wright's article in the Jour. Path. and Bact., 1925, 28, p. 541.

² Embolic glomerular nephritis was first described by Lohlein (1910). Gaskell, then Baehr (1912 and 1921) extended these observations and more recently Warwick (1922) discussed the subject. A study by Clawson (1926) claims that in rabbits focal glomerulonephritis, similar to that associated with human subacute bacterial endocarditis, was produced experimentally by directly inoculating the rabbit's heart with fine ground-up suspensions containing very tiny particles of agar and clumps of anhemolytic streptococci. Clawson, however, did not establish that mechanical plugging of the glomeruli from ground-up agar alone (without bacteria) failed to cause the lesions; one cannot say, therefore, if the focal damage is due to mechanical plugging or if the organisms are essential in the production of this embolic injury.

Lohlein: Med. Klin., 1910, 6, 375.

Baehr, G.: Jour. Exp. Med., 1912, 15, 330; Amer. Jour. Med. Sci., 1912, 144, 327.

Warwick: Jour. Lab. and Clin. Med., 1922, 7, 507.

Clawson: Arch. Path., 1926, 1, 911.

not necessarily imply an error or fault in blood-culture technic. With the advent of newer and improved methods in blood-culture, organisms are being found more frequently, and these methods may uncover a bacteremia in some cases now labeled "bacteria-free."

Following upon an early or initial bacteremia the blood may become sterile quite suddenly, the disease, nevertheless, continuing to a fatal end. The entire picture takes but a few months. At autopsy the heart vegetations yield myriads of bacteria. We must, therefore, evaluate a negative blood-culture here as a sign of a quickly approaching death and not as an augury of amelioration or recovery.

Occasionally the bacteria-free stage is comparatively prolonged, and the disease seems to be arrested. The unwary observer, consequently, might mistake a negative blood-culture in a case of apparent steady clinical improvement as safe ground for proclaiming a good prognosis. But, in reality, while symptoms abate, these patients succumb just the same, sometimes before fever is gone entirely. The afebrile course is striking. Few or no bacteria are found in the heart lesions.

According to Libman, still another form of subacute bacterial endocarditis with a bacteria-free stage may follow upon the heels of an unsuspected dormant, streptococcal (viridans) heart valve infection. Such persons have been known to carry on their tasks like well people; they are presumably well, capable even of severe exertion. Quite dramatically they are struck down by an overwhelming infection; fever, leukocytosis, petechiæ, and bone tenderness are soon noted. Careful study can disclose information pointing to a long-continued and unappreciated illness, *i. e.*, malaise, or feelings of chilliness or complaint of "not feeling well," etc.; in some instances there may be changes of the facial coloration and even alterations in the heart sounds. The blood can remain sterile, but the rapidly unfolding clinical aspects stigmatize this picture as bacterial endocarditis.

Libman also has called attention to a type of subacute bacterial endocarditis, bacteria free, and apparently healed. He considers this:

The Healed¹ Phase of Subacute Bacterial Endocarditis.—The active subacute bacterial heart affection may subside, fever disappearing for months or permanently; these patients are considered cured. The spleen stays large, the anemia is pronounced (high retention nitrogen figures if uremia), petechiæ are seen in half the cases, also "café au lait" pigmentation and endocarditis symptoms. The blood is spontaneously rid of bacteria, the heart lesions showing advanced organization and healing, and the kidneys showing healed embolic glomerular lesions. Accordingly, these afebrile patients have had clinical and pathologic features suggestive or corroborative of subacute bacterial endocarditis, but are no longer in an active stage, while cardiac and renal alterations remain. *In these healed cases a constant finding is a sterile blood-stream.* Or, to express it differently, *the absence of anhemolytic streptococci from the circulation in afebrile cases and seemingly clinically "burnt out" cases of subacute bacterial endocarditis suggests strongly that there is a related subacute or chronic glomerular nephritis (healed embolic lesions) which may terminate in uremia.* This observation holds also for the "unhealed" cases of subacute bacterial endocarditis when the blood remains bacteria free over a long period of time.

In the main, then, we may summarize the significance of anhemolytic streptococcemia for the conditions enumerated above as follows:

1. Nearly all clinically active cases of subacute bacterial endocarditis have a positive blood-culture.
2. In these active cases the blood-cultures may be positive constantly or sporadically or negative persistently after a single or repeated appearance of bacteria. The clinician must differentiate between these cases and the arrested types showing a sterile blood-stream.
3. The diagnosis of subacute bacterial endocarditis may be conclusive from its clinical aspects alone or a positive blood-

¹ Recoveries have been reported by:

Libman, F.: Amer. Med. Jour., 1920, 2, 304. Lecture under auspices of Med. Soc. of Kings Co., New York, pp. 246-274, P. Hoeber, 1923, 1924 series.

Murry, L. M.: Ann. Clin. Med., 1922, 1, 18.

culture may be essential to incontrovertibly establish the correct diagnosis.

4. For certain clinical phases of subacute bacterial endocarditis, *i. e.*, the bacteria-free stages and the healed conditions, a negative blood-culture supports (does not negate) the diagnosis.

5. When the blood-stream remains sterile for a long time the clinician should suspect the presence of a complicating embolic glomerular nephritis.

B. Acute Bacterial Endocarditis.—*In acute bacterial endocarditis we are not to expect anhemolytic streptococci in the blood-stream.* This form of endocarditis lasts a short time—a few weeks, six to eight at most—and is characterized by its rapidity, with death as an almost inevitable end. Most commonly the blood contains hemolytic streptococci, pneumococci, staphylococci, gonococci, but other bacteria may be the causative agent, among them very occasionally the anhemolytic streptococcus. Generally this latter organism is not virulent enough to produce the overwhelming condition and fatal outcome observed in acute bacterial endocarditis.

II. THE OCCURRENCE OF ANHEMOLYTIC STREPTOCOCCI IN RHEUMATIC HEART AFFECTIONS

It is the generally held opinion that rheumatic endocarditis is a distinct condition, yet, according to some investigators, whose work is not universally accepted, rheumatic and bacterial endocarditis may possess an identical etiology.¹

A. The Relation of Anhemolytic Streptococcemia to Acute Rheumatism of the Heart.—The presumption of those workers who claim the identity of these two conditions is that anhemolytic streptococci are responsible for the vegetations and clinical consequences of acute rheumatic infection,² and this con-

¹ See references to Clawson and collaborators.

² Combs, C. F. (Brit. Med. Jour., 1920, 2, 306; also Quart. Jour. Med., 1922, 15, 114) claims to have produced the rheumatic type of endocarditis with *Streptococcus viridans*. See also the interesting experimental studies of Thalheimer, W., and Rothschild, M. A. (Jour. Exp. Med., 1914, 19).

The following citations deal with the finding of *Streptococcus viridans* in the blood, joints, or exudates of rheumatic endocarditis cases:

tention is supported by bacteriologic data and by the ability of the organism to cause in rabbits experimental endocarditis and myocarditis claimed to be similar to human rheumatic endocarditis. Clawson and Bell (Arch. Int. Med., 1926, 37, 66) maintain that bacterial lesions differ from rheumatic only in the intensity of the inflammatory reaction. The process of healing is always present, but complete healing is rare, and, in their opinion, even the clinical stigmata of rheumatic infection, *i. e.*, pericarditis, joint manifestations, etc., can arise in subacute bacterial endocarditis. Thus, they write that acute pericarditis occurred in 22.5 per cent. of their 80 cases of subacute bacterial endocarditis and in 72 per cent. of their 18 cases of acute rheumatic endocarditis. Pericarditis was present in only 18 per cent. of their patients with healed (presumably rheumatic) valvular disease. The authors duly stress the fact that 59 per cent. of their bacterial cases had developed upon old healed valves (probably of rheumatic origin), but in their minds they are clear that an associated pericarditis can occur in subacute bacterial and in rheumatic infection of the heart, and is, therefore, not a differential feature.¹

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- Beaton, R. M., and Walker, E. W. A.: Brit. Med. Jour., 1903, 1, 237.
 Beattie, J. M., and Yates, A. G.: Jour. Path. and Bact., 1912, 17, 538.
 Camisa, G.: Centralbl. f. Bakt., 1910, 57, 99.
 Collins, F. R.: Brit. Med. Jour., 1913, 1, 220.
 La Fetra, L. E.: Arch. Ped., 1915, 32, 135.
 Loeb, L. M.: Arch. Int. Med., 1908, 2, 266.
 Poynton, F. J., and Paine, A.: Lancet, 1900, 2, 861.
 Quigley, W. J.: Jour. Infect. Dis., 1918, 22, 198.
 Rosenow, E. C.: Jour. Infect. Dis., 1914, 14, 61.
 Swift, H. F., and Kinsella, R. A.: Arch. Int. Med., 1917, 19, 381.
 Walker, E. W. A., and Ryffel, J. H.: Brit. Med. Jour., 1903, 2, 659.
 Westphal, Wassermann, and Malkoff: Berl. Klin. Woch., 1899, 36, 638.

¹ This relationship has an important bearing on any consideration which attempts to delineate the special form of subacute bacterial endocarditis, "atypical or indeterminate type," as an entity *sui generis*. Libman and Sacks (Arch. Int. Med., 1924, 33, 704) published a detailed description of 4 cases with autopsy findings of what they considered a hitherto undescribed form of valvular and mural endocarditis. The patients were young people, ten and a half to thirty-seven years of age, and had suffered from no previous heart trouble. They ran a subacute course with fever and advanced anemia; the signs and symptoms in part were typical of subacute bacterial endocarditis and for rheumatic endocarditis as well, but there were enough reciprocally

If Clawson and Bell, for example, are right, then anhemolytic streptococci in the blood-stream with endocarditis may signify also an acute rheumatic infection, although it is generally accepted and understood that in the greatest majority of cases an anhemolytic streptococcemia does not accompany an acute rheumatic endocarditis. The organisms are recovered from the blood of a rheumatic case where they assailed an endocardium previously damaged by rheumatism, or where they entered the blood-stream of a patient with old standing rheumatic heart disease at some moment when the rheumatic infection flared up again, or when a terminal invasion carried them into the circulation. For the time being it is perhaps safer to reach no definite conclusion as to whether or not anhemolytic streptococci can produce acute rheumatic endocarditis. A discovery of the etiology of rheumatism, obviously, would aid in clearing this point. Until then one should be cautious, in certain borderline cases, in accepting or rejecting an anhemolytic streptococcemia as a direct and chief cause of the endocardial damage in rheumatic situations.

B. Combined Rheumatic and Subacute Streptococcal Endocarditis.—Clinically we can differentiate rheumatic and bac-

contradictory details to impugn the validity of diagnosis of either condition. For example, as against rheumatic infection and in favor of subacute bacterial endocarditis there were skin lesions (some simulating lupus erythematosus), petechiæ with white centers, Osler's nodes (in 1 case), emboli (excluding any possible particle freed from a left auricle thrombus), an enlarged spleen, generalized purpura, and an acute or subacute diffuse glomerular nephritis. On the other hand, suggestive and, in fact, strongly pointing to a rheumatic infection and against a bacterial heart affection, were the severer joint disturbances, the heart valve lesions, and the presence of an acute fibrinous pericarditis. All four valves were attacked (strangely, the tricuspid did not escape in any case), the heart muscle contained no discernible Aschoff bodies found in rheumatism or Bracht Waechter nodes found in subacute bacterial endocarditis, and cultures from the crushed valves' vegetations were sterile. Unlike the vegetations in rheumatic endocarditis, where the verrucæ are small, rather firm, and strung along and confined to the valve closure line, in this "atypical endocarditis" the verrucæ were larger, softer, of irregular size, fastened to the valve by a broad base, the lesion spreading to the heart lining of the auricle and ventricle, or spotting the endocardium in isolated small patches. *No anhemolytic streptococci were recovered in the blood of these cases.*

terial endocarditis, and combinations of both, and our conception of the rôle the streptococci play will depend upon which view we hold with reference to a single or double etiology of these conditions. We have already spoken of the vulnerability of heart valves, injured by rheumatism, to superimposed infection from anhemolytic streptococci. Excepting a very rare discovery of a simultaneous initial rheumatic fever and subacute streptococcus endocarditis (Libman reported such a case established by bacteriologic and pathologic studies), our attention is now directed to the occurrence of streptococci (anhemolytic) in the blood-stream of patients who have already had rheumatic heart involvement, the infection disappearing the heart damage remaining. Here the patient may be acutely or subacutely ill from an exacerbation¹ of rheumatism and the streptococcemia becomes a confusing phenomenon often misdirecting the clinician's interest. Such a patient is sick from rheumatism and the positive blood-culture speaks for a secondary invasion either as a terminal flourish, or else it denotes an escape of bacteria into the blood-stream from some focus of infection unrelated to the rheumatism.

If the strains of anhemolytic streptococci recovered from subacute bacterial endocarditis possessed pathognomonic traits, as against those discovered elsewhere, we would have a method for ascribing the true influence which these organisms play in these respective conditions. As it is, the diagnosis is governed chiefly by the clinical course and symptoms, and the clinician must be prepared to recognize an anhemolytic streptococcemia, in this connection, as a possible transient manifestation. At the same time it is not possible to say when an accidental find of these organisms in the blood really represents a true bacterial endocarditis engrafted upon an old rheumatic process, the significance of which becomes established with the subsequent progress of the malady.

We have, then, three chief considerations of these bacteria in connection with rheumatism:

¹ The term "acute exacerbation" may refer to the rheumatic fever as a general infection of the patient or to a lighting up of the site of infection in the heart.

1. Are they directly implicated in the cause of some cases that appear to be rheumatic endocarditis?
2. Are they secondary and, therefore, in a sense inconsequential invaders of the blood-stream?
3. Are they always the specific cause of subacute bacterial endocarditis and of this disease only, even when rheumatic symptoms are or have been present?

DISCUSSION

Anhemolytic streptococci, as already observed, by their absence or presence in the blood-stream may serve as important factors in determining the diagnosis and prognosis of many forms of endocarditis. These bacteria also have a particular interest for the clinician in auricular fibrillation and in the so-called "atypical or indeterminate type" of endocarditis.

1. The Relationship of Anhemolytic Streptococcemia to Auricular Fibrillation.—If the cardiac rhythm is altered to produce auricular fibrillation subacute bacterial endocarditis does not occur, despite the fact that the patient may have had for a long time a heart damaged and made vulnerable by rheumatism, syphilis, or arteriosclerosis (auricular fibrillation is also associated with Graves' disease). This strange observation has been corroborated by many clinicians. It is, therefore, pertinent to state that a negative blood-culture is the rule in almost any situation where an auricular fibrillation appears. We do not know if the blood develops any specific bactericidal properties or whether organisms cannot remain in the circulation because of a faulty mechanical pump, or whether subacute bacterial endocarditis in some peculiar form, for example, does occur here after all, but stays undetected.

2. The Relationship of Anhemolytic Streptococcemia to the So-called "Atypical or Indeterminate Type."—We have discussed the peculiar clinical syndrome described under this name. This may be a mixture of two conditions, *i. e.*, rheumatism and the bacteria-free stage of subacute bacterial endocarditis, representing a clinical entity for which a negative blood-culture would be, as it were, a constant and expected feature. Of course, in con-

sidering this type as a distinct one it must be recognized that an acute rheumatic process of the heart readily, although imperceptibly, can pass into a (superimposed) subacute bacterial infection, the latter asserting itself as the overwhelmingly dominant picture. Moreover, at times a very mild case of subacute bacterial endocarditis cannot be distinguished from a rheumatic endocarditis, and perhaps, most important of all, it must be remembered that hearts crippled by rheumatic infection are very vulnerable to bacterial infection. The physician consequently may have spread before him at one time unmistakable signs of bacterial infection together with the signs of rheumatic valvular disease (Biggs believes that the clinician may often find it impossible to distinguish subacute bacterial endocarditis from rheumatic endocarditis),¹ but this "atypical type" of endocarditis begins with a symptom pattern possessing distinct yet incomplete delineations of both these conditions. And there is no antecedent story of rheumatism. That the blood-stream at some time may have anhemolytic streptococci cannot be excluded; on the other hand, however, even if anhemolytic streptococci were recovered from the blood, we should be at a loss whether to ascribe the cause of the condition to the bacteremia or to interpret the presence of the bacteria as a secondary invasion.

The observer obviously must be on guard when he meets features of rheumatism and subacute bacterial endocarditis in the same patient, and he must evaluate a constantly negative blood-culture result here in the light of two salient factors: (1) this type of "indeterminate endocarditis" does not represent an old rheumatic crippled heart upon which a bacterial process was superadded, no bacteria presumably entering the blood-stream, and (2) the sterile blood-culture results are not to be considered as negative blood-culture findings in so-called healed cases or in clinically indisputable instances of subacute bacterial endocarditis bacteriologically unproved.

In general, we have followed the classification of Libman because in his aim to separate the various conditions of subacute bacterial endocarditis as definite types (not phases) he has helped

¹ Biggs, A. D.: Arch. Int. Med., 1925, 35, 402.

to a clearer understanding of the entire disease. To our mind, however, one should be cautious in assigning a separate niche to any group syndrome when the disease itself assumes so rich a variety of pictures. The seeming random invasion of the blood-stream by bacteria, the variation in tendency and occurrence of embolization with its apparently haphazard localization, the process of local healing in the heart lesions—these fundamental features may be predestined by the anatomic architecture of the blood-vessels as an example, for instance, and not by any factors of infectivity or immunity¹ response relative to the causative organism.

But a bacterial infection does play an active important part in subacute bacterial endocarditis; it is not a secondary invader. Organisms reach the heart lining, produce soft friable, large, irregular sized verrucæ. An inherent capacity for healing, present in all inflammatory processes, exists here also, so that occasionally the cardiac lesions go on to complete healing containing living bacteria, but sealed off from the blood-stream. Obviously, clinical manifestations will depend upon the condition of the local heart lesions (thrombi formation, bacteria content, fibrosis, etc.), upon the dissemination of embolic metastases from these lesions, and upon the invasion of the blood-stream by bacteria.

With this in mind it is not difficult to envisage bacteria-harboring verrucæ tightly sealed and then suddenly weakened at some spot, and so breeched for the escape of bacteria into the circulation. Conversely, bacteria-laden lesions might shed organisms intermittently into the blood, the lesions then healing completely so that no more bacteria could enter the blood-stream, those remaining in the heart lining becoming destroyed or per-

¹ We are aware that immune bodies supposedly function to help healing and cure in this disease. There is no unanimity of opinion concerning these bodies produced by anhemolytic streptococci, although in some quarters (references below) specific agglutinins, complement-fixing bodies, and opsonins have been described in subacute bacterial endocarditis.

Clawson, B. J., and Bell, E. T.: *Arch. Int. Med.*, 1926, 37, 66.

Kinsella, R. A.: *Arch. Int. Med.*, 1917, 19, 367.

Libman, E.: *Jour. Amer. Med. Assoc.*, 1923, 80, 813.

Tunnickliff, R.: *Jour. Infect. Dis.*, 1909, 6, 346.

manently entombed. We have, therefore, no absolute assurance that repeatedly negative blood-cultures signify more than a sterile blood-stream during the period of blood investigations. A fleeting bacteremia of some undiscovered moment cannot be ruled out.

FOCAL INFECTIONS AS A RESPONSIBLE CAUSE FOR ANHEMOLYTIC STREPTOCOCCEMIA

A dormant or active focus of infection or inflammatory process anywhere in the body may contain anhemolytic streptococci. Bacteria may reach the blood-stream, but spare the heart valves. From practically any streptococcus-containing focus the blood may be contaminated, *i. e.*, the tonsils and Waldeyer ring, teeth sockets and roots, thrombosed veins (lateral sinus), lung abscess, the hilus of the lung, phlegmons, osteomyelitis, gall-bladder, appendix, adnexia, also in postpartum conditions. The signs, etc., depend upon the site of the focus, and the positive blood-culture, without clinical manifestations of subacute bacterial endocarditis, indicates strongly that the respective focus of infection is responsible for the blood-stream contamination. What has been said before applies here also, namely, that a seemingly innocent anhemolytic streptococcemia accompanied by a focal infection may be the first (and unappreciated) feature of a subacute bacterial endocarditis. This is very rare. The disappearance of the focus of infection goes hand in hand with the disappearance of the bacteremia, and these patients remain well and free from cardiac and embolic manifestations. We report one case to illustrate how a recurrent anhemolytic streptococcemia disappeared when the primary focus healed, in this instance a post-tonsillectomy lung abscess, and the patient recovered completely.

Case I.—A. A. (No. 11,027), a female Italian worker, aged twenty-eight years, entered the New York Post-Graduate Hospital March 6, 1926, ten days after a tonsillectomy, when she complained of cough, expectoration, and fever. For the immediately preceding two years she had been caring for her husband who was ill with active phthisis, and after his death, for six weeks

prior to the removal of her tonsils, she was "below par," losing 11 pounds in weight.

In the hospital she had fever (102° – 104° F.), leukocytosis, a systolic heart murmur, and signs of right upper lobe involvement (these focalized later as for a lung abscess). x-Ray confirmed the lung abscess diagnosis and from her blood (March 9, 1926) *Streptococcus viridans* was cultured. Three days later her blood yielded comparatively few colonies. April 3d she was transferred to the Burke Foundation where she gained 10 pounds. On May 13th she returned for examination. Her lung signs had disappeared, her temperature was normal, and her blood-culture sterile.

Similar experiences have been published to call attention to the recovery of anhemolytic streptococci from the blood of patients with focal infections. For instance, Aschner¹ says: "Up to July, 1912 no case of blood-stream invasion by anhemolytic streptococci was recorded at the Mount Sinai Hospital except in cases of subacute endocarditis."

"In the course of one year's routine blood-culture examinations during the course of a year I isolated anhemolytic streptococci in 4 cases which presented no evidence of infective endocarditis. One case (No. 4343) was an osteomyelitis of the mouth, where Horder finds *Streptococcus salivarius*. Another (No. 4316) was a case of postabortion infection, in which I obtained hemolyticus. Here the infecting organisms came undoubtedly from the intestinal tract, where Horder finds *Streptococcus fecalia*. In a third case (No. 4049), an abacterial polynuclear-celled pleural effusion, 3 colonies of anhemolytic encapsulated streptococci were obtained from the blood. The fourth case (No. 4348B), a meningitis due to *Streptococcus mucosus*, yielded 2 colonies in the blood-culture plates. One colony was a typical *Streptococcus mucosus*, the other was an anhemolytic streptococcus. I cannot say definitely whether this was a case of mixed infection (the meningeal infection was pure) or a case of mutation of the organism in the blood-stream, but I am inclined to favor the latter view.²

¹ Aschner, P.: *Jour. Infect. Dis.*, 1917, vol. 21.

² For classification of streptococci see Blake, F. G.: *Jour. Med. Rev.*, vol. 31, p. 99.

"The finding of such organisms in the blood of patients not suffering from subacute endocarditis was a new experience at the hospital laboratory. It might be feared that this would lessen the diagnostic value of the blood-culture in subacute infective endocarditis, but the function of the laboratory is to confirm a diagnosis suspected from the clinical symptoms. Where other courses of bacteremia can be excluded and where sufficient clinical phenomena are present, the finding of anhemolytic streptococci in the blood still indicates the existence of an infection of the endocardium. According to our own experience, the finding of anhemolytic streptococci in the blood-stream usually indicates an infection of the endocardium."

A review of the literature contains few definite reports of a similar nature. Josephine Walker¹ reported a case of *Streptococcus viridans* septicemia with recovery within two months. Six weeks after the beginning of the patient's illness the blood-culture was positive. The author is not clear whether endocarditis was present, nor does the publication state whether the patient really had bacterial endocarditis.

Warren and Herrick² reported 10 cases of *Streptococcus viridans* bacteremia in a variety of clinical conditions, *i. e.*, lung abscess, typhoid fever, arthritis, bronchitis, otitis. Nine of these cases recovered completely. The authors found subsequent blood-cultures negative in 1 case, but they do not mention whether or not the bacteremia persisted in the other 9 cases, nor are there any data regarding later clinical observations or follow-up. Their cases seem to belong in the group of conditions where the bacteremia is related to a definite focus of infection.

IV. PREAGONAL INVASIONS BY ANHEMOLYTIC STREPTOCOCCI

In any number of circumstances anhemolytic streptococci are found circulating in the blood; thus, in various types of endocarditis, in neoplastic diseases, in Hodgkin's disease, in specific infections like typhoid and paratyphoid, etc., the physicians may be startled by an unexpected bacteremia. It is difficult to state

¹ Walker, J: *Women's Med. Jour.*, January, 1917.

² Warren and Herrick, A.: *Jour. Med. Sci.*, April, 1916, p. 556.

whether this signifies a mechanical liberation from some dormant or quiescent nidus, or whether the debilitated state of the patient makes it easy for these organisms to gain access into the blood of the host. Striking is the dearth of response to the presence of these organisms, and in some cases criteria for judging if there be a response or not is masked by an already existing pyrexia, leukocytosis, toxemia, etc. Such a bacteremia, however, is generally seen in patients with lingering and severe illnesses, with no marked leukocytosis, perhaps with no endocarditis, and certainly with no tenable evidence that we are dealing with a bacterial endocarditis. The following 2 cases illustrate this point:

Case II.—L. R. (No. 9145), a white man twenty-four years old, had generalized Hodgkin's disease in June, 1925. (A cervical lymph-node was removed at the New York Post-Graduate Hospital, and the diagnosis established.) Through the summer and early fall he received deep x-ray therapy. In December he returned to the hospital with pronounced signs and symptoms of Hodgkin's, running a high intermittent fever. He was not especially prostrated. A few days before his death (January 19, 1926) he developed a remarkable blood condition of complete agranulocytosis with a leukopenia which fell quickly from 2800 to 240 total white cells.¹ The blood-culture demonstrated many colonies of *Streptococcus viridans*. The autopsy disclosed extensive granulomatosis throughout the body and multiple hemorrhagic infarctions of both lungs. These pulmonary lesions contained innumerable clumps of anhemolytic streptococci around which there was not the slightest sign of tissue response (Figs. 107, 108). The heart valves were not involved.

Case III.—Dr. A. (referred by Dr. C. F. Jellinghaus), a physician seventy-one years old, in excellent health and of robust build, accidentally fell and injured his right hip. There

¹ I am indebted to Dr. H. Shattuck for the privilege of reporting this case. Because of its striking blood-picture it has been published in full in a discussion of leukopenia in Hodgkin's disease.

was no fracture, but directly thereafter he had difficulty in extending this limb and he could not walk without the aid of a crutch or cane. A month later he began to complain of malaise and vague pains in all his limbs. Examination at this time sug-

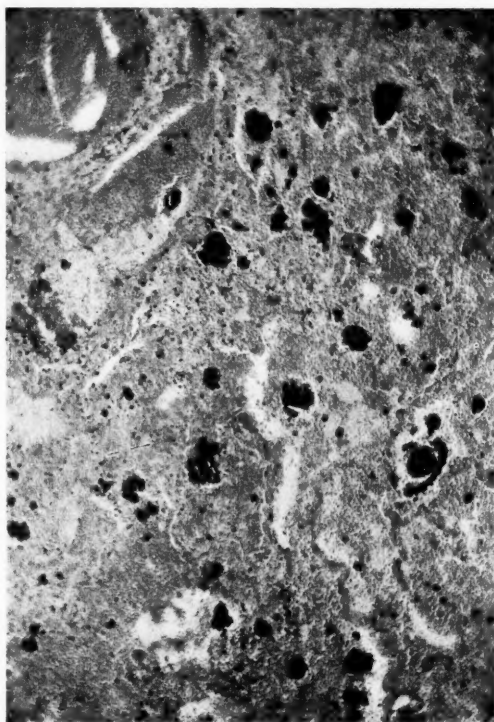


Fig. 107.—A low-power magnification of L. R.'s lung parenchyma, showing clumps of anhemolytic streptococci with no surrounding inflammatory process.

gested that the patient was ill with a mild influenza, but his fever continued and soon touched a higher level, while he became bedridden and developed bradycardia and anemia with a moderate leukopenia. The Widal tests were negative for typhoid and paratyphoid, and the blood-cultures was negative

also. A fortnight later a second blood-culture was negative again. Three weeks later and five days before death the blood

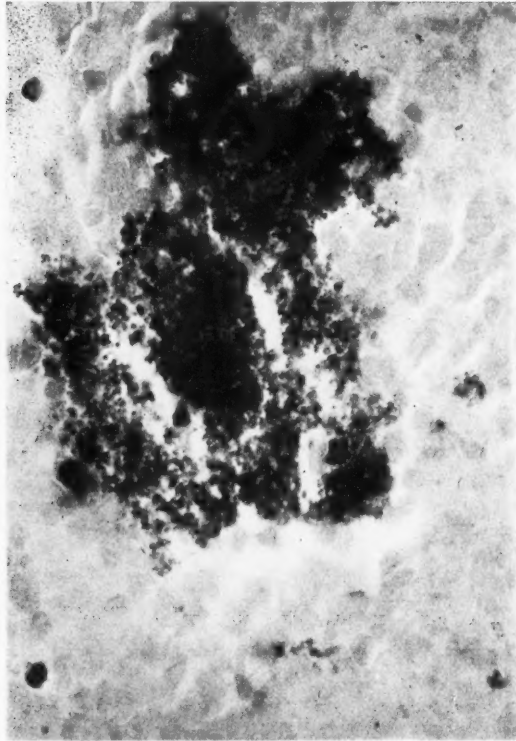


Fig. 108.—A high-power microphotograph of Fig. 107.

contained paratyphoid (B) bacilli and *Streptococcus viridans*. (This was confirmed independently by Dr. A. L. Garbat two days later.) No autopsy was obtained.

V. TRANSIENT ANHEMOLYTIC STREPTOCOCCEMIA

Students of bacterial endocarditis have all had to deal with rare instances when the blood-cultures alone or the blood-culture first directed attention and interest to a diagnosis of bacterial

endocarditis. These workers suspected also that the entrance of anhemolytic streptococci (viridans) into the blood could be transitory and unassociated with any lesion of the heart and unaccompanied by any detectable focus of infection. In other words, a bacteremia from no ascertainable focus might suddenly appear, and then as dramatically vanish, leaving the host unaffected.

Case IV.—T. Mc. (No. 7652), an Englishman, aged twenty-four, was admitted October 25, 1925 to the New York Post-Graduate Hospital and discharged November 7, 1925. He was a rather well-preserved man and stated that three weeks prior he had had pains in his head, chest, and back, also spots on his shins. During these weeks he was sleepy, sweated a great deal, and had jerky movements of the limbs. His illness began with malaise, chill, fever, and a sore throat. The next day his right knee was painfully swollen and remained so for three days. He discovered small tender nodules over the anterior surface of his legs and thigh. Fever lasted for two or three days. A day before his admission to the hospital he vomited. He gave a vague history of having had what he considered rheumatism in his shoulders three years ago.

He was flushed, febrile, and perspired freely. On his chest and abdomen there was a rather poorly defined roseola (this and the sleepiness, we surmised, were caused by bromides which he had been taking). His tonsils were large and had some purulent discharge. His teeth showed caries and pyorrhea; his lips and fingers were cyanotic. The pulse rate was 60, the blood-pressure 124/74, and there was a faint systolic murmur over the base and apex of his heart. His neck was very slightly rigid. The blood-count was: red blood-cells 4,160,000; white blood-cells 20,000; poly. 89 per cent.; platelets 377,000. The Wassermann reaction and blood chemistry figures were normal; the spinal fluid was negative on culture, but contained 46 white cells per cubic millimeter, of which 90 per cent. were lymphocytes. For three days his fever ranged from 98° to 101° F. On the fourth day he was afebrile and normal in every way, and stayed so for eleven subsequent days while in the hospital. November 7th

his blood-count was 7400; poly. 59 per cent. The blood-culture taken on the day of his admission was reported positive for non-hemolytic streptococcus and the subculture positive within the next day. The colonies were numerous and not all random in occurrence. A second blood-culture taken one day after the first one remained sterile for eleven subsequent days.

We have here a patient who came into the hospital acutely ill with fever, leukocytosis, and a systolic heart murmur. The house physician considered him, upon admission, a case of early rheumatic endocarditis, but influenza seemed very probable. The very sudden vanishing of bacteria from the blood-stream within twenty-four hours, strikingly associated with a subsidence of all clinical symptoms, a return to a normal white cell count, and the disappearance of the heart murmur all emphasized the likelihood that we were observing a transient bacteremia unrelated to endocarditis or to any focus of infection of any clinical import.

We cannot be entirely certain that the blood-stream invasion did not come from the tonsils or teeth after all, nor can we, without the necessary lapse of time, report upon the eventual outcome in this case. However, enough has been detailed to indicate that this transient bacteremia left the patient unharmed, and in all probability represented an evanescent blood invasion whose cause is unknown.

A case of similar nature (*Streptococcus viridans* septicemia and recovery) is reported by King, J. T. Fr.¹ King's report deals with a negress who had coarctation of her aorta and who had *Streptococci viridans* in her blood on several occasions from February 7, 1925 to March 30, 1925. In June, 1925 her blood was sterile and she had gained in weight and was well.

Oille, Graham, and Detweiler published a series of cases of anhemolytic streptococcemia. The temperature was normal or subnormal; all these patients recovered. In 1924, nine years after their original description, they traced 20 of their 23 patients, all of whom were free from signs of subacute bacterial endocarditis.

¹ Arch. Int. Med., 1926, vol. 38, 69.

Salus had 18 cases resembling those described by Oille, Graham, and Detweiler. Both groups seemed to be epidemic. None of these cases exhibited endocarditis.

Observations of a like character have been reported by Biggs, Capps, Major, F. J. Smith, and Libman. In all these cases, however, there was no implicated focus of infection, there was no rheumatic story of any direct bearing, and no foundation for considering the bacteremia a terminal invasion.

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CONTRIBUTION BY DRS. GAYLORD W. GRAVES AND
CHARLES WINFIELD PERKINS

NEW YORK CITY

**THE THYMUS CONSIDERED WITH REFERENCE TO
THE ADVISABILITY OF ITS ROUTINE x-RAY IN PEDI-
ATRIC SURGERY***

THE study of the thymus is beset by so much that is problematic that one might expect a discussion relating to this organ to attempt the establishment of some fact very positively. The aim of the writers, however, is simply to review certain well-known facts which are frequently disregarded, and if possible to define more accurately conclusions which are being formulated with uncertainty by the average clinician. The work of Crotti¹ has provided much that is here recited.

From the time when Vesalius and Bartholinus, about the middle of the seventeenth century, gave the first pictures and descriptions of the thymus it has been the subject of varying speculation. Successive generations were taught that this gland was the center of courage and affection (*θῦμος*), that it was a supplementary organ of milk secretion, that it was a nerve organ linked with the medulla, that it was a lymphoid organ, and an epithelial organ. Even so-called cavities in the structure, now known to be artifacts, engaged the attention of anatomists as late as the end of the eighteenth century. The developmental history of the organ is, therefore, highly important.

Its derivation embryologically is from the prolongation of epithelium of the third (occasionally also from the fourth) branchial cleft. Close relationship developmentally with the

* Presented in part before the Section on Pediatrics of the New York Academy of Medicine, March 11, 1926.

parathyroids and the thyroid accounts for occasional thymic inclusions in the thyroid, and to some degree probably for the association of hyperthyroidism in certain instances of thymic enlargement. Cells composing the cortex of the thymus are regarded as largely lymphocytic. In the medulla lymphoid cells are less numerous, and here are found the distinctive Hassal's

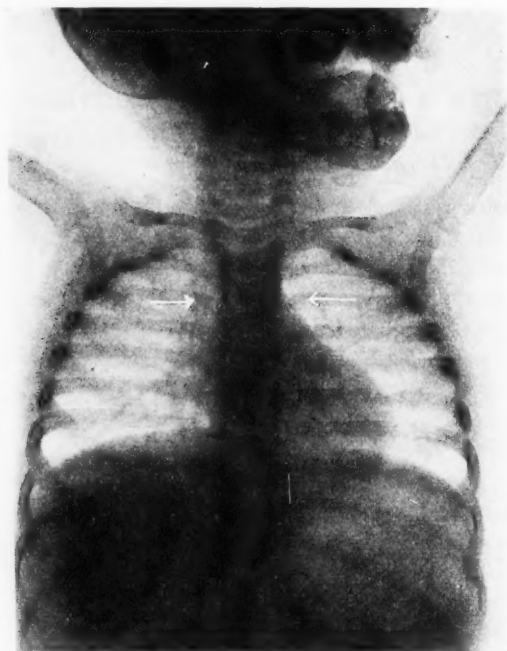


Fig. 109.—“Normal” appearance. Female infant, ten months old, weighing $13\frac{1}{2}$ pounds.

corpuscles which Hammar¹ has considered as derived from the reticular cells of the medullary substance which have an epithelial origin. Authors who look upon the thymus as a lymphoid organ are divided into two groups, one believing that the epithelial cells of which the gland is at first chiefly composed undergo transformation to thymic cells resembling or identical with

lymphoid tissue; the other, that the organ is essentially lymphocytic as the result of invasion of lymphocytes from the mesenchyme.

It is to be noted that in nuclein the thymus is nearly five times as rich chemically as the lymph-nodes, as shown by Ivor and Bangs in 1904, and that the phosphorus content is correspondingly high, the rôle of the gland in phosphorus metabolism

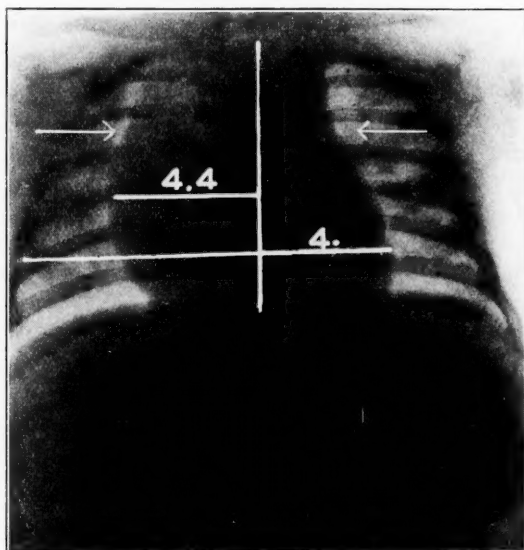


Fig. 110.—Hypertrophied thymus in an infant aged eight months.

being comparable to the rôle of the thyroid in the metabolism of iodin.

Anatomically, Hammar has divided the various types of thymus into three classes—cervical, thoracic, and cervicothoracic. The thoracic type is typical in man. Yet not uncommonly in man the cervical portion is of exaggerated formation. In its relations the organ is in contact with the sternum anteriorly as low as the fourth intercostal cartilage. Posteriorly the thymus lies upon the right auricle and may touch the esophagus and

tracheal bifurcation with close attachment to the left innominate and close approximation to the vagus and inferior laryngeal and phrenic nerves, particularly the right. The pericardial sac and posterior surface of the thymus capsule are usually adherent. The arterial supply is derived from the large thoracic vessels, and this supply is said to be richer than the venous drainage. There is a lymphatic drainage by which any secretion of the gland can finally reach the blood-stream.

How essentially the thymus belongs to the period of most rapid growth and development is indicated by its weight variations. From birth to two years the weight ranges from 7 to 10 grams, glands of 20 to 30 grams in the first year being regarded as definitely hyperplastic. Some authorities believe that the size is greatest at two years; others, at puberty. Hoskins³ has shown that in its ratio to the body size the gland is seven times as large at birth as at puberty. Considerable divergence in the weight figures assigned by different investigators is apparent:

	Hammar in Osler's Medicine. Grams.	Delafield and Prudden. ⁴ Grams.
Birth.....	12	13
1- 5 years.....	23	23
6-10 years.....	26	37
11-15 years.....	37.5	}10 to 20 yrs. 25
16-20 years.....	25.5	
After twenty years' gradual atrophy.		

By many observers relatively large thymus *x*-ray shadows in infant subjects are considered usual.

Studies of thymic function have been based principally on extirpation experiments following the work of Restelli⁵ in 1845. Feeding experiments also have been conducted, and the morphology of the gland has been observed under various conditions. By acute disease atrophy is induced. Consequently autopsies performed upon adults who have met death suddenly are most reliable. Dustin⁶ has shown that even in the adult soldier the gland is rarely atrophic. The theory that extirpation induces rickets has been shown to be without foundation. Likewise the

statement that excision exerts a deleterious effect on skeletal development, genital growth, and psychic maturity has been denied. Even the part ascribed to the gland in skeletal growth is in doubt because the skeleton grows not only when the thymus is large but also when it is most rapidly decreasing in size between the fourteenth and eighteenth years. After 75 carefully

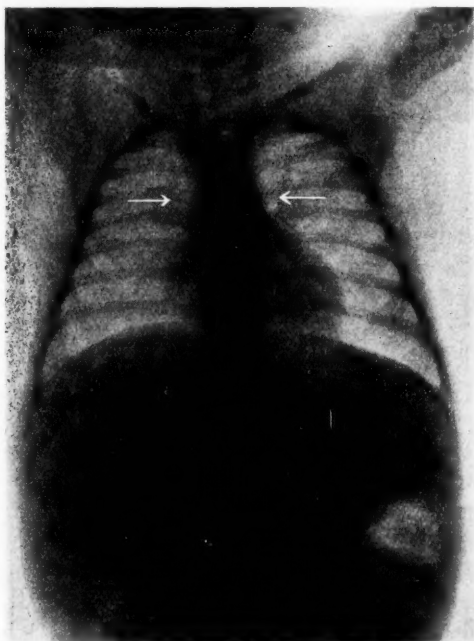


Fig. 111.—Negligible thymic shadow in male infant of three months, weighing $7\frac{3}{4}$ pounds, whose birth weight was 5 pounds.

controlled experiments with thymectomy on animals Park and McClure⁷ published conclusions that the thymus is not essential to life and that its extirpation produces no detectable alterations in experimental animals. The possibility of delay in closure of the epiphyses and of changes in endocrine organs immediately after thymectomy was not excluded.

In a review of 24 articles appearing from 1904 to 1924

C. L. Short⁸ of the Harvard Medical School stated conclusions recently cited by Mosher⁹ as follows:

1. The thymus is not necessary to life.
2. Thymectomy has no effect on the growth and development of the skeleton and organs.
3. Castration delays the involution of the thymus.
4. A substance contained in the thymus when injected causes convulsions.
5. Thymus feeding to salamander larvæ with parathyroids causes tetany.
6. Thymic hyperplasia follows double suprarenalectomy.
7. Thymic hyperplasia in thyrotoxicosis is secondary.
8. In birds a relationship exists between the thymus and the egg-producing mechanism.
9. So-called "thymic death" not due to tracheostenosis probably bears no relation to the state of the thymus gland.
10. One, if not the primary, function of the thymus is to produce leukocytes.
11. The thymus may also have an antitoxic function (Hammars).

The evidence on the whole is strong that the thymus is not a gland of internal secretion.* That it may serve as a manufactory and storehouse for lymphocytes at the time of life when there is greatest need to combat infection is a popular view. Preponderance of nuclein in the structure indicates that from this source may be derived something modifying metabolism and reinforcing immunity.

Persistence of the thymus to an abnormal degree is noted in exophthalmic goiter in about three-quarters of the cases, the thymic enlargement being possibly compensatory. In Addison's disease, acromegaly, myasthenia gravis, and rickets the thymus persistence has also been remarked.

The association of sudden death with thymic enlargement was reported early in the eighteenth century by Bichat. Early in the nineteenth century Kopp described thymic asthma. In

* In the index of Dodd and Dickens' late work on the Chemical and Physical Properties of the Internal Secretions¹⁰ the thymus is not even listed.

1858 Friedleben denied the possibility of production of laryngospasm by enlarged thymus, and thenceforth controversy became acute, numerous authorities insisting that the symptoms emphasized by Kopp were due to direct mechanical pressure, and



Fig. 112.—Thymic shadow rated as suspiciously larger than normal in two weeks' old female infant weighing 5 pounds, 6 ounces. (Weight at ten weeks $7\frac{1}{4}$ pounds.)

others considering excess of thymus secretion the cause. In 1889 Paltauf's studies established the association of enlarged thymus with general lymphoid hyperplasia, arterial hypoplasia, and (in older patients) chlorosis. This condition became known as status lymphaticus.

The clinical picture in cases of thymus hypertrophy is so often observed and described that one need only recall that:

(a) Thymic stridor may be manifest at birth and show varying degrees of intensity with intervals during which it is not in evidence, the paroxysms occurring as breath-holding and "rage spasm" seizures or as asthma.

(b) Dyspnea may be constant and persistent.

(c) Sudden death with lymphatism demonstrable only at autopsy may occur without previous warning.

(d) Convulsions simulating tetany may constitute the only key to the condition.

(e) Even with marked thymic enlargement nothing untoward may occur at any time.

In addition to the susceptibility to sudden death, abnormal susceptibility to infection and psychic instability are characteristically observed in thymic subjects.

The oldest theory to explain the sudden death of such individuals was that of mechanical pressure from the enlarged gland. Although this explanation is scouted by many as unscientific, it cannot be disposed of in all instances even on scientific grounds.

Crotti notes that pressure may take place at two points. One coincides with the superior opening of the thorax, into which the thymus is drawn on hyperextension of the head and on coughing, by the ligamentous attachment of the thymus to the thyroid, the anteroposterior diameter of this opening in young infants being not over 2 to 3 cm. The other point at which pressure may occur is between the innominate, the left common carotid, and the cross of the aorta.

Another popular explanation for a long time used to account for fatal cases in which the factor of enlarged gland pressure could be proved non-operative was based on the arterial hypoplasia which was supposed to permit cerebral hemorrhage under slight strain. This view, too, has proved unsatisfactory.

Equally inadequate have been the theories that the thymus elaborated a toxin of some sort which under certain predisposing states, such as anesthesia, trauma, or infection, produced collapse and death.

Symmers¹¹ ingenious theory of anaphylaxis to account for

these cases has been current for nearly ten years, but as the result of experiments in sensitization has lost much of the support at first accorded it. This theory holds that necrosis occurs in large numbers of germinal follicles in the lymph-nodes with resulting sensitization of the body by a specific nucleoprotein thus formed. When at a suitable period the tissues are again

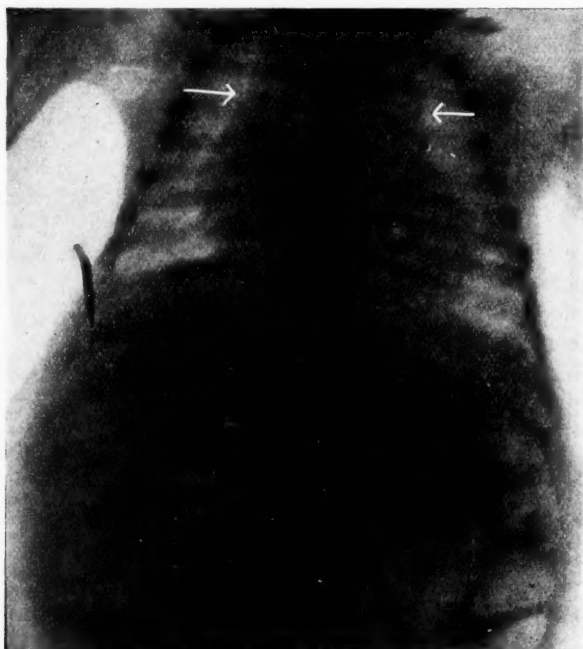


Fig. 113.—Thymic enlargement in a child aged three and a half months.

subjected to the action of the same protein derived from nuclear dust formed in the same type of tissue the anaphylactic reaction is completed. Pappenheimer's¹³ emphasis on the marked disintegration of nuclear material as evidenced by the thymus probably has contributed foundation to Symmers' theory.

Yokoyama¹² in 1913 showed that injections of extract of thy-

mus were hypotonic and lessened the action of adrenalin on the blood-pressure.

Tracy¹⁴ has laid emphasis on superabundance in the blood-stream of thymic hormone, with insufficiency of the adrenals.

Mosher has remarked a similarity between death from acidosis and that observed in status lymphaticus.

Very recently McLean and Sullivan¹⁵ have observed at the Babies' Hospital in New York a pronounced hypoglycemia with suprarenal insufficiency in 3 fatal cases of thymic convulsions in infants. They remark the similarity of the collapse in these cases to that seen in insulin shock.

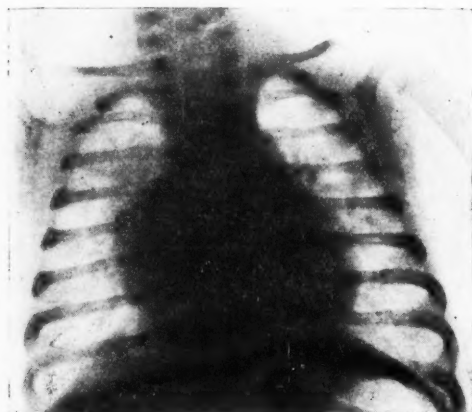


Fig. 114.—Congenital heart abnormality in an infant aged three months. Note narrow base of the heart. This patient had marked cyanosis and stridor, with no heart murmur, and the case was mistaken for one of an enlarged thymus before Roentgen examination was made.

Disturbed chemistry dependent upon endocrine imbalance certainly offers an explanation more plausible than others for the collapse observed in thymic cases. Just as the metabolic disturbances from goiter may be disproportionate to the size of the thyroid (although a large thyroid most commonly excites suspicion of true hyperthyroidism), so hyperactivity of the thy-

mus, predicated upon the theory of a secretory function, might exist independently of actual anatomic thymus enlargement.

Reuben and Fox¹⁶ "feel that sufficient evidence has not been adduced to prove (1) that the thymus is the cause of the so-called thymic syndrome in every case; (2) that the syndrome is due to hyperplasia or enlargement of the gland; (3) that there is an absolute correspondence between actual size of the gland and x-ray picture of it."

From a mass of detail of which such extracts are illustrative, it is well-nigh impossible for the clinician to derive much that is practical. It is readily apparent, however, that three conditions require to be differentiated to which the following descriptive terms are applied: thymic enlargement without involvement of the general lymphatic system, status lymphaticus without thymic enlargement, and status thymicolymphaticus (of which the name is sufficiently descriptive). It is essential to remember that the dyspnea of tracheostenosis is undoubtedly mechanically possible from thymic pressure and that even without enlargement a child may exhibit the condition of general adenopathy described by Paltauf, with arterial hypoplasia and diminished resistance to infection, anoxemia, and trauma.

If one could investigate every case of sudden death unexplained by known lesions, including those in the first weeks of life ascribed to atelectasis and congenital cardiac disease without murmur, those in infancy due to unexplained convulsions, those occasionally following the administration of antitoxin, those resulting from anesthesia, trauma, and minor surgery (such as thoracentesis), he would gain a most enlightening conception of the frequency of the complex and rarely recognized condition which we are considering. The Collective Investigation of Status Lymphaticus* now being conducted in the British Isles will undoubtedly go far to make possible such a conception. In this connection Symmers' report is suggestive. Of 5652 autopsies at Bellevue, status lymphaticus findings were present in 457, or 8 per cent. Of the 457 only 92 were under twenty years of age.

* Secretary, W. Howel Evans, Liverpool.

Practically, although enlargement of the thymus may exist without status lymphaticus or any observed clinical disturbance, nevertheless hyperplasia of the tissue of the thymus quite uniformly constitutes the key to the general pathologic condition. In 118 cases of Symmers' series selected as true examples of status lymphaticus, the thymus was hyperplastic in every in-

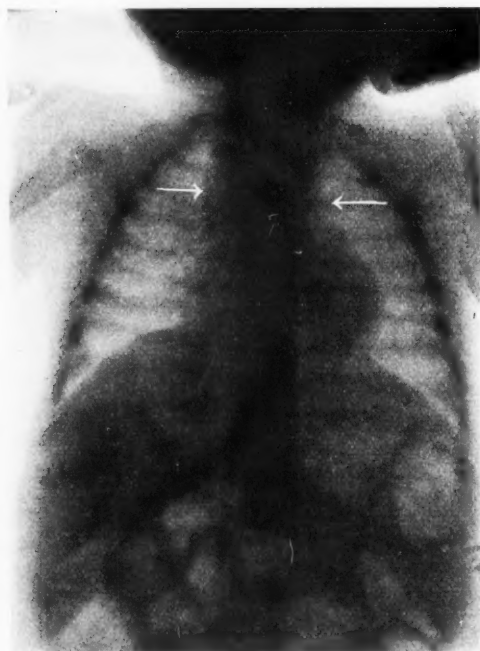


Fig. 115.—Large thymic shadow in male infant under six months. No clinical manifestations.

stance. Whether or not the child subject clinically presents features suggestive of status lymphaticus, enlargement of the thymus is to be considered as evidence favoring the diagnosis of this underlying state, and whatever be the rôle of the enlarged thymus, the finding of an enlarged mediastinal shadow not interpreted as other than that of the thymus, with or without

dyspnea, suffocative attacks, and stridor, should uniformly arouse surgical caution.

This introduces as our practical problem the interpretation of the thymus x-ray and its importance in preventive pediatrics.

One is immediately confronted with a mass of semiconflicting literature on x-ray technic and interpretation too complex for a brief review. Among numerous writers who have given their expressions are Freeman,¹⁷ Quimby,¹⁸ Pfahler,¹⁹ Gaarde,²⁰ Grier,²¹ Friedlander,²² Drea,²³ De Buys and Samuel,²⁴ Gerstenberger,²⁵ Benjamin and Goett,²⁶ Blackfan and Lyttle,²⁷ Benjamin and Lange,²⁸ Liss,²⁹ and Perkins.³⁰

After all is considered one need only keep in mind the following chief points:

Exposures must be very short without blurring.

Typical variations in thymus shape, *e. g.*, exaggerated length with slenderness of shadow, thickness and broadness, anomalies of position and relation must be considered.

Positive evidence is valuable; negative evidence not final.

Dr. John B. Parsons³¹ has discussed the difficulties of x-ray diagnosis:

The thymus may be cervical, cervicothoracic, or thoracic, the last position being most common. The position varies with inspiration and expiration and to some extent with diastole and systole. He notes that in ordinary radiographs of the chest a shadow beneath the sternum represents great vessels and mediastinal glands. Ordinarily this is only a little wider than the sternum. If the shadow is definitely wider, enlarged bronchial glands, enlarged thymus, or anomaly of great vessels is to be considered. If the thymus is long and narrow, but thick and large, an anteroposterior view might be negative. During systole and with the diaphragm contracted and up at the end of expiration, a long thick thymus no wider than the sternum might be pushed up together with other mediastinal structures, assuming a position nearer the chest wall, and thus appear large upon x-ray.

Liss, in 42 per cent. of a group of 119 newborn infants, found

a shadow suggesting a thymus more than 3 cm. in measurement, and this without gross symptoms.

Peterson and Miller³² state that abnormally enlarged thymus occurs in 40 to 50 per cent. of newborn infants.

Greenthal,³³ after an analysis of 2000 consecutive cases ranging from three days to twelve years of age, admitted to the University of Michigan Hospital, reported thymic enlargement in 90, or 4.5 per cent. Eighty-seven gave no history or symptoms.

During the past four summers a tonsil and adenoid operative service has been maintained at Seaside Hospital by St. John's Guild of New York, in connection with its general pediatric service, comprising 175 beds. The throat service, under the direction of Dr. Floyd McDaniel, in the four seasons has conducted about 2000 tonsil and adenoid operations with the loss of 1 patient whose case will be cited as exemplifying thymic death. Under the same anesthesia employed for the tonsillectomy a resident dentist has routinely extracted bad teeth. Ether has been employed almost without exception and suction apparatus has facilitated the work. No lung abscess has been known to have occurred and in only 1 case did pneumonia develop. One boy developed a suppurative appendicitis with perforation about forty-eight hours after tonsillectomy, but prompt surgery gave him an uneventful recovery.

The occurrence of the single fatality fairly early in the series of operations in the case of a colored boy whose thymus at autopsy weighed 54 grams, prompted Dr. Rowland G. Freeman in 1924 to advise preliminary x-ray of all cases before operation, with a view to the recognition of those which might fall under the hazard of thymic enlargement. As a result the hospital has already acquired a large collection of chest x-ray films of children who were presumably fairly normal, as well as a considerable amount of corresponding material derived from cardiac and pulmonary cases.

In 1924 the occurrence of the death, during anesthesia, of a little colored girl undergoing orthopedic surgery, whose preliminary chest x-ray had not been interpreted as indicating thymic enlargement before operation, but was felt by Dr. Free-

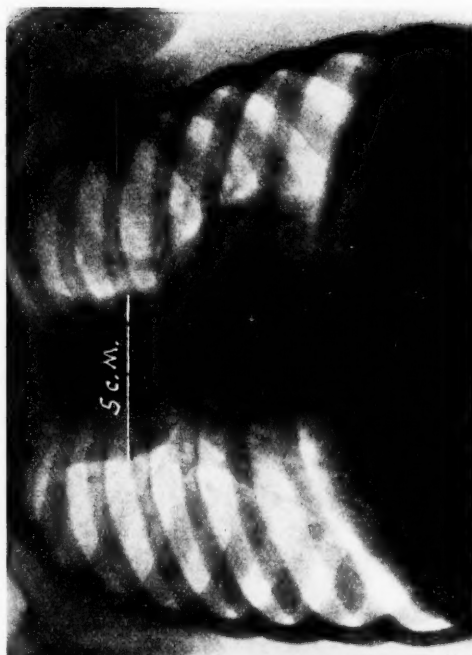
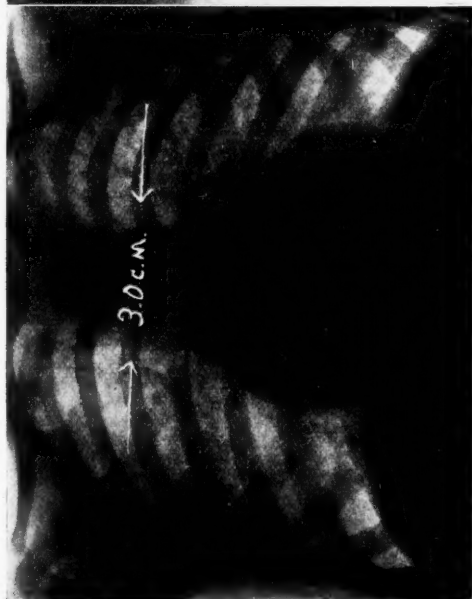


Fig. 116.—Normal heart and thymus in a child aged three years. Fig. 117.—Enlarged thymus in a child aged three years. Note bulging shadow at base of heart.

man to have revealed an abnormally large shadow (Fig. 120) reawakened interest in the significance of mediastinal shadows in our cases and prompted the writers to review about 700 films obtained for the most part in the routine work above described.

A necessarily arbitrary standard was employed as a basis for estimates in interpreting these films. When three observers* agreed that a large shadow was very probably due to actual thymic hypertrophy, the case was so rated. When only two

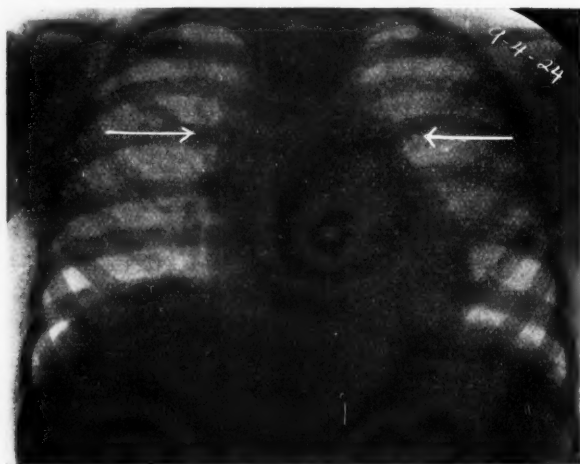


Fig. 118.—Hypertrophied thymus in a child aged five years. This patient is a sister of the one represented in Fig. 117.

of the three so agreed the case was listed as doubtful. The plates were all postero-anterior views. If objection be made that no measurements served as criteria in the estimates the answer may be made that the two groups, first, one of doubtful cases; second, one of apparently definite cases, did at least constitute a collection from the series representing distinct departures from the ordinary *x*-ray findings. From the reproductions herewith presented the reader may perhaps judge concerning the accuracy of the estimates. It would appear that these estimates

* The writers and the *x*-ray technician.

were conservative, perhaps, in the light of reports from other sources, too conservative.

At any rate, in this series of 700 films obtained from children between one and seven years of age, thirty were rated as showing definite thymic enlargement, and an equal number as showing doubtful enlargement. In the latter group the orthopedic patient whose x-ray was negatively interpreted, but whose thymus at autopsy weighed 39 grams, was included.

On the supposition that infants at this hospital would show a higher incidence of enlarged thymus than older children, as indicated by the reports of observers elsewhere, a review of a small series of 28 chest x-rays was made, all of the subjects under one year of age, 70 per cent. being under six months. Of this series 3, or 10.7 per cent., were rated as showing definite thymic enlargement, and 4, or 14.3 per cent., as showing suspicious enlargement. An explanation of the low incidence observed in this group may exist in the generally known fact that a state of malnutrition or illness may conduce to recession in the thymus. These early cases which were taken at random from the ward included several acutely ill infants and the weight figure average for the group of 28 is estimated at about 3 pounds below normal for age. Accompanying illustrations (Figs. 109, 111, 112, 113) exemplify the extreme differences noted in this group.

On a review of the histories belonging to the "positive" thymus cases it was possible to arrive at only a few significant facts.

In at least 5 an operation under anesthesia was performed, or had been performed prior to the patient's admission, without ill effect. In not more than 1 of the 5 had x-ray treatment preceded operation. In only 1 case was there history of convulsions, dyspnea, or other symptoms suggesting thymic abnormality. Whooping-cough was a possibility in this instance. One child had received 2500 units of diphtheria antitoxin without ill effect. In a group of 18 in which the complete history was available, 6 had rickets, 5 had had pneumonia, 12 had definitely enlarged tonsils. General lymphadenopathy was in no instance noted.

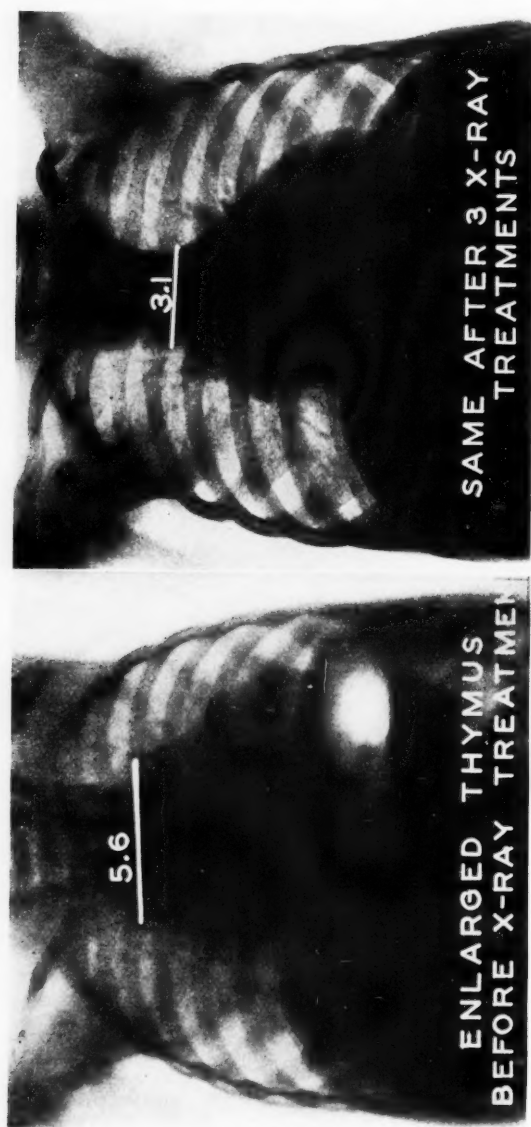


Fig. 119.

The cases were almost equally divided between males and females. The age limits were thirteen months and seven years in the positive group beyond one year of age, the average in this older group being one year and five months.

In any case awaiting tonsillectomy or other surgical operation, when there was x-ray evidence of thymic enlargement, the routine procedure was to cancel operation and institute x-ray therapy for the purpose of reducing the size of the organ. In most of the cases in which this procedure was begun the child did not remain in the hospital long enough for the operation

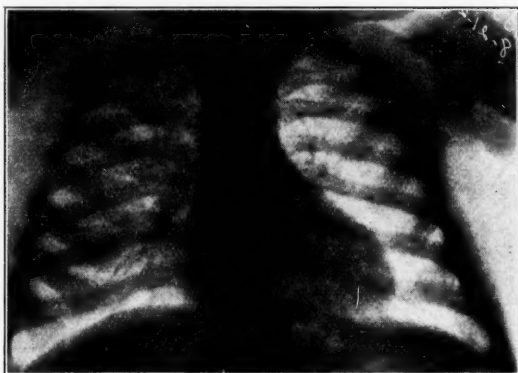


Fig. 120.—Patient had a low placed enlarged thymus which did not show definitely in the Roentgen examination. This child, whose age was four years, was operated upon and died in the advanced stage of anesthesia.

to be performed, this fact being in part accounted for by the shortness of the service. Figure 119 illustrates the effect of three treatments in an individual case.

Observations at Seaside Hospital thus indicate that between the ages of one and seven years about 8.6 per cent. of all children may show mediastinal shadows suggestive of thymic enlargement, and about 4.2 per cent. show a considerable increase in the thymic shadow beyond normal; that a certain number of cases exemplified by the orthopedic case in which x-ray was not recognized before operation as significant may have the poten-

tiality of sudden fatality without being suspected; and finally, that a certain number of cases showing an enlarged shadow do withstand infectious disease, operation under anesthesia, and serum administration without apparent ill effect from the thymic condition. That, however, so considerable a percentage exhibit evidence of an enlarged thymus and that this condition may carry with it operative risk, as indicated by records of many thymic deaths in the past, when autopsy corroboration has been positive, strongly indicates that preliminary *x*-ray of the thymus in childhood may well be employed routinely in

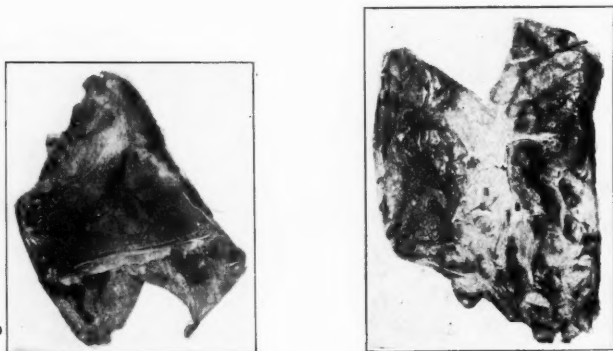


Fig. 121.—Anterior and posterior views of the postmortem findings of the subject shown in Fig. 120. Very large thymus weighed 39 grams. The gland was situated so low over the heart that it could not be shown by the Roentgen examination.

surgery as a reasonable measure of safety. To put the matter concretely, if of 1000 operative cases in children, 40 or 50 show definite *x*-ray evidence of thymic enlargement, there is a perfectly good chance that postponement of operation for the 40 or 50, to permit of a period of careful observation combined with *x*-ray therapy, may save a life or two. It seems certain that 40 or 50 out of 1000 is a very conservative figure for the large shadow cases. Some of these possibly are cases of status thymicolymphaticus. Some may be potential cases of tracheostenosis.

Incidentally, a comparison of the figures indicating the incidence of enlarged thymus in the small group of 28 infants who were malnourished with the figures of other observers tends to strengthen the teaching that prolonged illness and malnutrition conduce to diminution in the gland.

Into the difficulties of universal preoperative x-ray of the thymus, as a routine measure in pediatric surgery, one need not go. The feasibility of this step has been demonstrated and the advantage of heart and lung x-ray is obvious. It has always followed that when something could be proved desirable in medicine for the better protection of the patient, such an advance would be demanded and eventually would become routine.

The writers acknowledge invaluable assistance from Drs. Mawhinney and Mader of the x-ray department of St. John's Guild.

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"SUBACUTE" NEPHRITIS¹

CASE I

THE following is a synopsis of the clinical history and course and the pathologic findings in a case of "subacute" nephritis.

E. K., female, age eight, history No. 7761. Admitted to New York Post-Graduate Hospital October 29, 1925.

Past History.—The only previous diseases are whooping-cough and "abscess" of the right ear in the summer of 1923; occasional "colds"; headaches for the last six years; these are of moderate intensity and last all day, they are not present every day, but come irregularly; her mother claims that there has been some impairment of vision for one year. (Eye-grounds are negative at the present time, indicating that there must be another cause than nephritis responsible for the dim vision); no throat affection at any time; teeth always decayed and there has been constant troublesome stomatitis.

Present History.—The child's underclothes were slightly blood stained seven weeks ago; shortly after this the urine was frankly blood tinged; a few days later, September 7th, feet, abdomen, lumbar region, and face became swollen; the attending physician ordered the child to bed on a salt- and meat-free diet; the swelling disappeared. One week ago fever and cough developed.

Course in Hospital.—Left upper lobe pneumonia, completely resolved November 11th.

¹ From the Department of Medicine and the Department of the Laboratories of the New York Post-Graduate Medical School and Hospital.

Edema gradually developed into marked anasarca; the extent of this may be judged from the fact that the weight increased from 52 pounds November 11th to 72½ pounds December 13th.

Uremic Symptoms.—On December 19th uremic symptoms began; they were as follows:

	December 19th,	20th,	21st,	22d,	23d,	24th,	25th,	26th,
<i>Bleeding gums</i>	x	x	x	x	x	x	x	x
<i>Vomiting</i> (including blood originating from esophageal erosion (see autopsy)).	x	x	x	x	x	x	x	x
<i>Twitching</i> (face, lips, eyes, extremities).	x	x	x	x	x	x	x	x
<i>Stupor</i>					x	x	x	x

Died December 26th.

Blood counts:

	Hemo- globin, per cent.	Red blood- cells.	White blood- cells.	Remarks.
October 30th.....	65	3,320,000	41,000	Pneumonia present.
November 6th.....	50	2,848,000	15,800	
November 9th.....			15,800	
November 14th.....	23	1,752,000	Secondary anemia marked
November 23d.....	32	2,556,000		November 18th, trans-
November 30th.....	39	2,508,000		fusion 240 c.c.
December 7th.....	40	2,176,000	6,200	

Wassermann reaction.—Negative.

Urine, Microscopic.—Until December 5th many red blood-cells, many pus and red blood-cell casts, occasional waxy and granular cast.

After December 5th many white blood-cells, a few hyaline casts, other elements had disappeared.

Albuminuria.—Constantly present to a marked degree.

Urine.—Specific Gravity.—Until the first of December most of the urine specimens showed a low specific gravity; however, in occasional samples the specific gravity was as high as 1020; after December 1st the following readings were found:

Date.	Specific gravity.	
December 2d.....	1012	Note the constant low specific gravity while there was marked anasarca and oliguria. This persisted for twenty-four days before death.
December 5th.....	1010	
December 6th.....	1012	
December 7th.....	1010	
December 8th.....	1010	
December 9th.....	1012	
December 10th.....	1010	
December 11th.....	1010	
December 15th.....	1010	
December 16th.....	1012	
December 18th.....	1010	

Blood chemistry:

Date.	Mg. per 100 c.c. blood.					Remarks.
	Urea N.	Uric acid.	Creat. inin.	NaCl.	Cholesterol.	
October 11th.....	63	Pneumonia October 22d to November 11th.
November 2d....	96	10.8	
November 4th....	134	486		
November 7th....	107	470		
November 9th....	82				
November 10th....	82	5.0	496		
November 17th....	65	3.8	526	240	November 18th transfusion 240 c.c.
November 24th....	56					
December 2d....	94	6.0	3.0	
December 7th....	110	December 2d to 14th, 265 gm. of urea by mouth.
December 9th....	156	3.0			
December 13th....	125	6.0	3.0			
December 22d....	213	9.6				
December 24th....	240	13.3	5.0			
December 12th—Serum albumin, 3.05 grams per 100 c.c.						
Serum globulin, 3.67 grams per 100 c.c.						
Serum protein, 6.72 grams per 100 c.c.						
Albumin, globulin ratio 0.83.						

Blood-pressure.—Highest of forty readings 115/80.

Died December 26, 1925, sixteen weeks after the onset of the acute nephritis.

Autopsy was performed four hours after death.

From the autopsy protocol only the following points of interest are recorded: Edema of the extremities and face, ascites. The heart is about the size of the subject's right fist, weight 120 grams, the valves are normal, heart muscle pale but firm. Both kidneys are slightly enlarged, 100 by 50 by 40; they are firm; the capsule strips without difficulty and the surface is smooth; the color is gray with numerous small pin-point yellow specks; on section the cortex is from 4 to 5 mm. wide, grayish white with yellow specks; the cortical markings indefinite; medulla without changes; the renal pelvis pale.

The esophagus shows a necrosis extending 15 cm. above the cardia; above that the mucosa is pale; a distinct ammoniacal odor is present.

The stomach contains mucinous blood-tinged fluid; the mucosa is red.

The duodenum and small and large intestine show marked edema and hyperemia of the mucosa.

Histology of the Kidneys.—The structure of the cortex has undergone conspicuous changes. The interstitial connective tissue is markedly increased and a pars radiata and convoluta cannot be differentiated. The strands of loose connective tissue

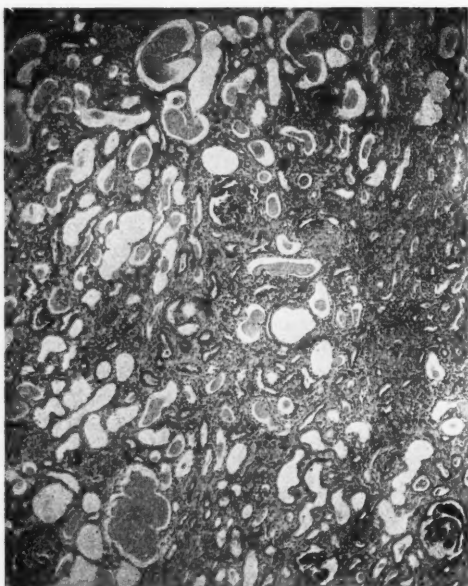


Fig. 122.—Subacute nephritis. The tubules are mostly dilated, their epithelial lining flattened, and they contained homogeneous casts ($\times 60$).

are diffusely infiltrated mostly with lymphocytes, sparingly with occasional plasma cells and sporadic polymorphonuclear leukocytes. Blood capillaries are rather scarce. Mononuclear cells containing blood pigment are frequently encountered. It is usually impossible to identify the individual tubules according to their position within the system of canaliculi. A great number of the tubules are dilated, their epithelial lining flattened, and their lumina contain homogeneous casts (Fig. 122). Among

the less dilated tubules two types can be recognized (Fig. 123). One, Type A, is lined by cells with distinct walls and round pale nuclei. Within the other, Type B, the cellular membrane can hardly be recognized; the number of cells is larger than in a tubule of corresponding size of the first type and the nuclei are darker. Dilatation of the lumen occurs in both types. Between

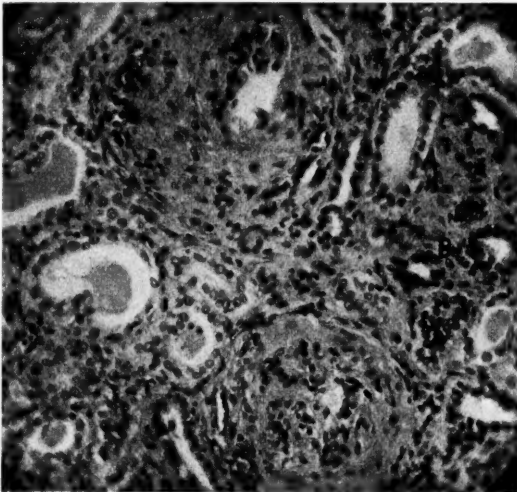


Fig. 123.—Subacute nephritis. Among the less dilated tubules two types can be recognized: A, Lined by cells with distinct walls and round, pale nuclei; B, lined by a larger number of cells having darker nuclei, and a poorly delineated cellular membrane. Malpighian corpuscles with more or less fibrosis predominate ($\times 260$).

these tubules which resemble most closely the collecting tubules of the normal kidney, occasional tubules of the convoluted type are found. Fat droplets are found at the base of the cells in numerous tubules and within the interstitial connective tissue. Only a minor part of the fat is double refractile. The epithelial cells of the remaining convoluted tubules show hyaline degeneration and frequently their lumen contains masses of necrotic cells. The interstitial tissue of the medulla shows far less cellular

infiltration and the tubules are less altered than those of the cortex. They contain occasional hyaline casts and polynuclear leukocytes. The ascending tubules of Henle's loop frequently show epithelial proliferation. All the Malpighian corpuscles are markedly altered; the vast majority of them have empty tufts; Bowman's space opposite the hilus of the glomerulus is

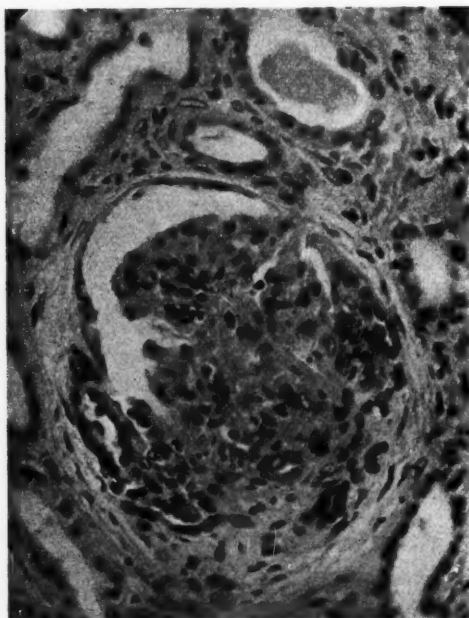


Fig. 124.—Subacute nephritis. "Epithelial crescent." Extracapillary glomerulitis ($\times 440$).

very frequently filled with a crescentic mass of proliferated epithelial cells (Fig. 124); the glomeruli are small, the capillary tuft plump, the capillary walls are thickened and the individual loops fused with each other; the number of the nuclei vary; glomeruli with a great number of nuclei of the endothelial and polynuclear leukocytic type are far less numerous than those where the number of nuclei is small; Malpighian corpuscles with

more or less fibrosis predominate (Fig. 123); in several of the corpuscles Bowman's capsule is lamellated and fibroblasts are growing between the proliferated epithelial cells; from the hilus, at the opposite side, fibroblasts extend into the convoluted capillaries of the glomerulus.

In analyzing the clinical and pathologic data there are two facts we desire to call attention to: the first is that an acute nephritis began sixteen weeks before death; the second is that death was brought on by renal insufficiency of a type characteristic of the terminal stages of a chronic nephritis.

The sudden onset with hematuria and edema and the subsequent finding of casts leave no doubt that this was an acute nephritis at the onset of the illness; during the period of observation the blood-pressure was low; however, it may have been elevated during the first few days of the disease and then dropped; on the other hand, an increase of blood-pressure cannot be demonstrated in many cases of acute nephritis. The pathologic data shows that there was no antecedent nephritic process, consequently this was not an acute exacerbation of a chronic renal disease, but was an acute affection of a previously healthy kidney.

The gradual increase in the blood urea was indicative of destruction of the glomeruli. In acute nephritis the blood urea does not increase unless the oliguria becomes extreme or anuria ensues; marked passive congestion of the kidneys may bring about a rise in the blood urea (we have seen one instance of 150 mg. of urea N per 100 c.c. of blood in which the kidneys showed only passive congestion at autopsy), but there was no passive congestion in this instance. The urea accumulated in the blood while the pneumonia was active; this is a common occurrence and may be ascribed to the protein destruction accompanying the pneumonia. Subsequently, the urea in the blood diminished rapidly until November 24th, after which time it again began to accumulate; this happened before the urea administration, as a diuretic was begun; the blood urea continued to increase after the urea medication was stopped, showing that the kidney—or the glomeruli—were no longer able to eliminate this substance adequately even though a low protein diet was instituted. The

specific gravity was low and fixed for the last few weeks of the disease. In cases of acute nephritis when the specific gravity becomes lowered it is an almost infallible sign that polyuria has appeared and the edema will diminish. In this instance there was no accompanying polyuria and the edema increased. This combination of symptoms, oliguria and a low specific gravity, pointed to the functional diagnosis of impaired glomerular (oliguria) and tubular (inability to concentrate the urine) activity, and pathologically to marked involvement of these structures. The anatomic examination showed the glomeruli to be largely destroyed and the tubules to be uniformly dilated and lined by a low flat epithelium.

The acute nephritis had, therefore, in a period of weeks become a chronic nephritis with a maximal renal insufficiency of such severity as to bring about a fatal termination.

There is one further point in the clinical course of this case that is worth noting. This is the disappearance of the red blood-cells from the urine on December 5th, three weeks before death. From the appearance, persistence, and disappearance of hematuria, as noted in this and in other cases, we believe that this symptom is of great value in guiding the treatment of nephritis and in formulating opinions regarding prognosis. If it is established that the blood in the urine originates in the glomeruli and is associated with a nephritis, then the hematuria signifies that circulation in the glomerular capillaries is going on; its cessation indicates either that the inflammatory glomerular lesion is subsiding or that the glomerular capillaries have been entirely closed by a process of organization, compression through exudate gathering within Bowman's capsule or occluded by the accumulation of inflammatory and proliferative material within the capillaries. Judging by the other clinical signs and symptoms, the persistence of oliguria and edema and the increase of the blood urea, in this instance it may be determined which of the two interpretations, normal or abrogated glomerular circulation, is to be accorded the disappearance of the red blood-cells from the urine. In the present patient, for the reasons mentioned, a serious import would be ascribed to this phenomenon and the

microscopic sections do show occlusion of most of the glomerular capillary tufts through hyalinization of the tuft and compression by proliferated cells—cellular crescents—within Bowman's capsule.

The reason for reporting this case is that in the American literature, as far as we have been able to ascertain, there is no similar instance. The pathologic texts furnish examples that are duplicates of the present kidneys, but the clinical monographs, except those evidently copied directly from European sources, have no instances of "subacute" nephritis and the conception of the term as given by them is very vague.

Volhard and Fahr present a most useful classification of glomerular (diffuse) nephritis, based on *clinical* grounds:

1. *Acute nephritis*.
2. *Chronic nephritis*, covering a period of the disease during which the ability to excrete the nitrogenous end-products remains normal and the kidney can concentrate the urine.
3. *Chronic nephritis*, terminal stage, when urea and other nitrogenous excretory products are retained in the body and the urinary specific gravity becomes low and fixed.

It is obvious that a case may pass from the first to the third stage very slowly or with extreme rapidity, as in the patient reported here. According to the time required from the onset of acute nephritis to its termination by renal insufficiency (provided the acute nephritis does not heal completely) Volhard has suggested a grouping of *chronic* nephritis from an *anatomic* point of view:

1. *Subacute nephritis*, characterized by a duration of weeks or months.
2. *Subchronic nephritis*, characterized by a duration of months or years.
3. *Chronic nephritis*, characterized by a duration of many years.

Applying these classifications to the present case, it is evident that, in the first place, the kidney condition, as revealed by the blood chemistry, is in the third or terminal stage of chronic nephritis; the progress of events has been so rapid that the dura-

tion from the onset of the acute nephritis to a terminal renal insufficiency is only a matter of sixteen weeks, hence the disease falls under the heading of subacute nephritis.

According to Löhlein, the first case of subacute nephritis was reported by Marchand in 1882; Löhlein gave the first extensive and thorough description of this condition in 1907. Since that time there have been no modifications of note made in the conception of this form of nephritis; the number of cases reported has been few, especially in the American literature. The description of these kidneys as given by Löhlein coincides very closely with that of the present case, Löhlein called such a nephritis "Stürmischer typus," and the course of this disease is truly a stormy one, since no therapeutic measures appear to stay the rapid progress of events in the least.

The glomeruli are usually anemic and collapsed; in some the cellular elements may be increased; the glomerular tufts are often hyalinized to a remarkable degree and with great rapidity (in one of Fahr's series of 4 cases hyalinization occurred within five weeks of the onset of the acute nephritis); the most marked and characteristic change of subacute nephritis is the large number of cells derived by proliferation from the inner lining of Bowman's capsule which become mixed with fibrin and leukocytes, and then are compressed so as to form the distinctively shaped epithelial crescent.

Fahr, as well as others, have described this as extracapillary nephritis in contradistinction to the more usual form in which the intracapillary changes predominate. It is probable that the speedy progress of the disease is due to the rapid involvement of the glomeruli and the cessation of their function. This is evidently brought on, in most instances, by the compression of the glomerular tuft through the epithelial crescent. In one of Fahr's 4 cases crescents were not found, and they were only slightly marked in 2 of Löhlein's 7 cases. From the clinical description of Fahr's report it is not clear that this subject did die of subacute nephritis, but rather of verrucous endocarditis and bronchopneumonia. It would seem, therefore, that the term "extracapillary" nephritis applies to all the instances of

"subacute" nephritis thus far reported. It is improbable that intracapillary involvement will result in the fulminating glomerular lesions characteristic of "subacute" nephritis.

The tubules, in all cases where they are mentioned, appear to be dilated and lined by a very low layer of epithelium. It is generally believed at the present moment that such alterations in the tubular structure are secondary to the severe affection of the glomeruli and the cessation of their function. The reported cases of subacute nephritis, as well as the present findings, substantiate this view.

The term "large white kidney" used to describe these cases is valueless, as large white kidneys are also present in other forms of nephritis.

Conclusion.—A case of "subacute" nephritis is reported. The clinical characteristics of this disease are: the initial symptoms of acute nephritis leading, within a few weeks, to death from renal insufficiency; the loss of renal function manifests itself by a marked rise in the blood urea (and other non-protein nitrogenous elements), in the blood (indicating loss of glomerular activity), a disappearance of red blood-cells from the urine (showing that circulation through the glomeruli is greatly impeded), and a low fixed specific gravity (due to diminished tubular function).

From the pathologic viewpoint all these cases have a marked involvement of the Malpighian corpuscles resulting from an "extracapillary" glomerulitis. Hyalinization of the glomeruli exists in many of these cases usually side by side with the glomerular crescents. Secondary to the glomerular involvement tubular changes appear. The tubules are dilated and lined by a very low layer of epithelium. These epithelial cells are uniform in appearance and have lost the specific characteristics attributed to the various tubular subdivisions, such as convoluted tubules, collecting tubules, etc.

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SYPHILIS OF THE ESOPHAGUS

ESOPHAGOSCOPY is frequently omitted in the study of esophageal disease. This is either because of a lack of knowledge of this procedure or because of an unfounded fear for it. How much more satisfactory it is to be able to make a diagnosis by direct inspection than by inference. And how much more satisfactory it is to look down into the esophagus and examine in detail the area of obstruction than it is to pass a bougie and feel blindly at a distance.

Carcinoma constitutes a very large percentage of esophageal lesions in adults, perhaps 95 to 98 per cent. It may perhaps be this preponderance of carcinomatous lesions of the esophagus that frequently influences the attending physician against a complete and thorough study of his patient. Because there may occasionally occur a condition of the esophagus which is not carcinoma, it is very important that such a condition should not be overlooked. Gumma of the esophagus, although rare, may however occur in a patient who is thought to have carcinoma; under such circumstances a hopeless prognosis is immediately changed to a favorable one. This is, of course, provided that the patient with the syphilitic lesion presents himself before he is ready to expire from the terminal stage of his disease.

The following case report will serve to illustrate: A male, white, age thirty-eight, was referred by Dr. I. W. Held for esophagoscopy. He was having difficulty with swallowing hard or dry food for the past three weeks. He localized the point of his difficulty to the region of the umbilicus. There had been no regurgitation or vomiting. Together with the feeling of temporary obstruction, he experienced slight pain when swallow-

ing hard or dry food. During fluoroscopic study a partial stenosis of the lower end of the esophagus was detected. The Roentgen film did not register any impression of the region of obstruction because the barium mixture passed through too quickly. The patient's condition was considered an early carcinoma of the esophagus, and he was referred for esophagoscopy. The esophagoscope, however, changed our impression. At esophagoscopy there was seen an umbrella-like convexity of the esophageal wall which appeared to be intensely red and slightly swollen. At the top of this bulge was seen a small dimple-like process which represented the esophageal lumen. On palpation with an instrument the esophageal wall seemed to be soft and was unlike anything which we had previously seen in the esophagus. A bougie, size 16 French, was readily passed through this area; it caused bleeding at once. We were dealing with a non-resistant stenosis. This type of stenosis we frequently find when a mediastinal neoplasm is pressing upon the esophagus. It was also noted that the aortic pulsation was abnormally prominent. Because the lesion was so unlike anything we had previously seen, the diagnosis of carcinoma was withheld. Whereas the patient denied a history of lues before esophagoscopy, he now admitted having had a primary lesion fifteen years before. In view of the history of the primary lesion, and because the esophageal lesion was strongly atypical for carcinoma, it was felt that we must rule out syphilis. Several specimens of blood were accordingly studied for their Wassermann reaction. Each time the report came back negative.

Upon his return home his physician gave the patient a dose of neosalvarsan. Within twenty-four hours he had lost his difficulty in swallowing. In addition to the neosalvarsan he was given mercury and potassium iodid by mouth.

He was again esophagoscoped three weeks later. Esophagoscopy now revealed a lower esophagus with an apparently normal lumen. There was no abnormality of color or texture, nor was there any constriction. The esophagoscope could now be passed into the stomach without difficulty. Nor was there bleeding at the time of the passage of the instrument. His blood

was again sent to the laboratory together with his spinal fluid. The Wassermann tests of these were reported back negative. At no time could we obtain a positive Wassermann reaction. It is well known that cases of syphilis are encountered in which the Wassermann reaction is persistently negative. The appearance of the lesion, the history of a chancre, and the favorable response to the administration of neosalvarsan leads to the conclusion that we were dealing with an early gumma of the esophagus.

Syphilis of the esophagus is not encountered frequently. Gastou, writing in Fournier's book on syphilis in 1906, collected 40 cases, of which 13 were verified by autopsy. Of these 13, at least half were of the hypopharynx or upper esophagus. In 1914 Wile reviewed the literature and added a case. His was the case of a female, aged forty, who had a history of dysphagia of eight years' duration. She was esophagoscoped by Canfield, who found a marked sclerosis of the entire esophagus with a stricture in both the upper and lower portions. She complained of pain and difficulty in swallowing. Wile makes this significant statement: "It is not improbable that many cases which die in cachexia, supposedly of carcinoma, are cases of death from marasmus as a result of syphilitic esophagitis." Guisez does not seem to agree with this. He has not encountered a proved case of this condition in over 3000 esophagoscopies. He feels that the use of the x-ray and the esophagoscope should have increased the frequency of the recognition of this lesion, and that it has not. However, the case recently reported by Jackson and his associates, together with the present one, and a case reported by McKinney before the American Laryngologic Association last June, would seem to indicate that we are beginning to encounter this condition with an increased frequency.

McMahon reports the case of a male, age sixty-three, who had had a primary lesion twenty-six years before. He presented himself with a complaint of difficulty in swallowing and loss of weight extending over a period of nine months. His Wassermann reaction was four plus and he experienced a recurrence after medication.

Bosch reported the case of a patient with gumma of the esophagus who died twenty-four hours after the administration of salvarsan. At autopsy a tracheo-esophageal fistula was found. This was due to the ulceration of a gumma through the esophageal wall. Gangrene of the lung was also present as a complication of this condition.

Jackson and his associates report the case of a man aged fifty-two, whose condition was previously diagnosed as carcinoma, and who proved to have an ulcerative syphilitic lesion of the esophagus. For three months he had progressive weight loss, dysphagia for solid foods, vomiting of blood, and tarry stools. Through the esophagoscope there was seen in the lower third of the esophagus a firm, rounded swelling, bulging in from the right and obliterating the lumen. In this instance an ulcerated surface could be made out. The Wassermann test was four plus. Antiluetic treatment stopped the hemorrhages from which this patient was suffering. A cicatricial stenosis due to healing, and occupying three-fourths of the lumen of the esophagus, was found at subsequent esophagoscopy. Normal function was restored by esophagoscopic dilatation.

The most recent case reported is that by McKinney. It is of unusual interest because both the lower esophagus and the pylorus were simultaneously involved in an ulcerative syphilitic process. A male, aged fifty-eight, presented himself with a history of difficulty in swallowing for the past two months. He had lost 40 pounds in weight, he was vomiting everything he ate, and could swallow only a tablespoonful of water at a time. He had considerable pain in the epigastrium. His blood Wassermann reaction was four plus. Fluoroscopy showed a stricture at the cardia with apparent infiltration anteriorly. At esophagoscopy McKinney found a marked constriction of the lower end of the esophagus. The anterior wall of the esophagus in the region was thickened, and presented a roughened surface, apparently an ulceration. Five days later the patient developed symptoms of collapse. His pulse became weak and rapid, his color was ashen, and he vomited a large amount of coffee-ground fluid; he died within a few hours. Autopsy revealed a con-

siderable thickening of the esophageal wall 3 cm. above the cardia. At the upper edge of this area there was an irregular perforation. Straddling the pyloric ring and involving the stomach and duodenum was found an ulcerative process consisting of two or more pockets extending through the wall of the stomach and duodenum, their bases presenting a bluish-white mass. Sections of the esophagus from the area of perforation, and of the pyloric region, showed the presence of epithelioid and lymphoid cells principally in the muscle layers, and an absence of surface epithelium. The pathologist reported syphilitic ulceration of the cardiac end of the esophagus and of the pylorus. It is unfortunate that this patient was seen in the last stages of his illness, for earlier recourse to the blood test and esophagoscopy might have brought timely and adequate therapy.

A majority of the patients in whom gumma of the esophagus occurs are males, although West reported 3 cases in females and Wile's patient was also a female. The age at which this type of lesion may occur corresponds to that age period during which the individual is prone to luetic infection. All the cases have occurred in adults.

As a rule, obstruction due to active syphilitic disease is comparatively free from symptoms. The symptomatology would seem to depend upon the stage at which the lesion is encountered. When encountered early in its development the only symptom may be difficulty in swallowing hard or dry food. As the duration increases and the ulceration advances bleeding may occur. Here, then, the anemia of the syphilis would be aggravated. Loss of weight would naturally follow. In the lesion that goes on to sclerosis, fibrosis, or cicatrization the obstruction will be more pronounced, and may be partial or complete. Or we may have a mixture of ulceration and firm infiltration and fibrosis with symptomatology corresponding to the extent of each type of tissue change in the lesion. Anemia, cachexia, and loss of weight come with more severe lesions, which have either lasted a long time or are of considerable extent.

In the differential diagnosis of esophageal lesions which cause obstruction it would be well to bear in mind that syphilis

of the esophagus is relatively rare, and that, being rare, it is likely to be overlooked. Carcinoma of the esophagus may for a time during its incipency present a picture very much like gumma. Recently a man, aged fifty-three, was referred for esophagoscopy. He was having some difficulty in swallowing solid foods and a slight loss of weight for the past four weeks. At this time it was impossible to make a diagnosis roentgenologically or with the esophagoscope, for there was no evidence of neoplasm. There was simply tumefaction and a convex bulge which was very soft. However, esophagoscopy two weeks later revealed the presence of a firm infiltrative process in the area of the previously observed tumefaction. In addition, the edge of this infiltration presented a fungating appearance, so that the diagnosis of carcinoma was readily established.

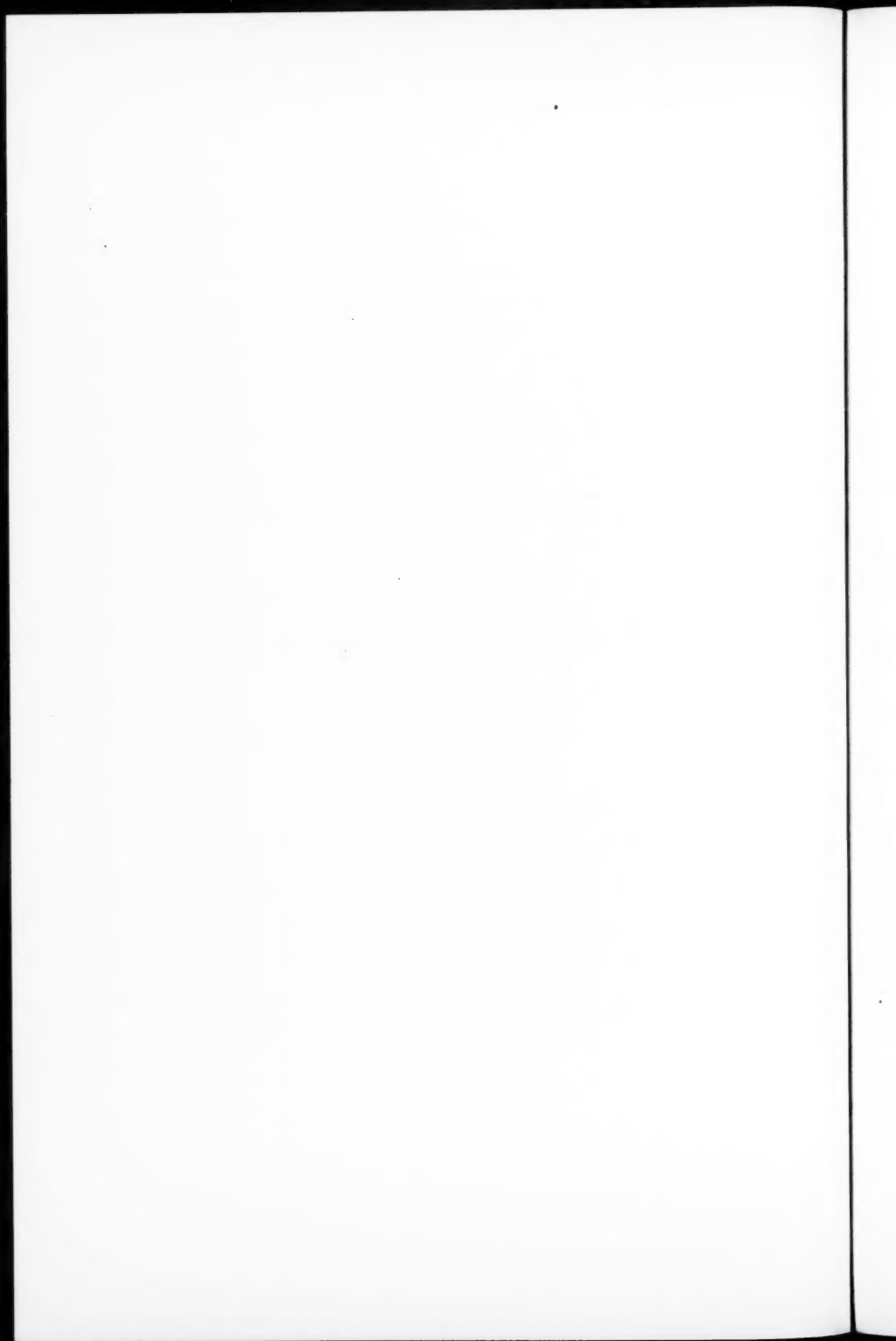
The progress of carcinoma is usually more rapid. In the ulcerative type of malignancy of the esophagus anemia and cachexia are very rapid in their development. We have seen a man in apparently good health enter the hospital with an ulcerative bleeding carcinoma of the esophagus to which he succumbed in less than ten days. Obstruction due to carcinoma causes the patient to abandon first solids, then semisolids, and finally liquids; the obstruction gradually increases until there is no longer a lumen remaining. Pain is due to the pressure of accumulated food at the site of the obstruction, and also in time develops as a result of extension of the process into the mediastinum, trachea, bronchus, or pleura. In syphilis the gumma causes difficulty in swallowing hard or dry food. Other types of food pass through the esophagus readily. As the gumma heals a resistance of the diseased area to the ready passage of food is developed. And this resistance may cause slight or partial, or grave and total obstruction. Progressive syphilitic disease is likely to cause cachexia. The gummatous process may ulcerate through the esophagus into the trachea, left bronchus, or aorta. Syphilitic cicatricial stenosis follows a pre-existing ulcerative lesion which is known to have healed. Of course the Wassermann test should be used in all atypical cases.

It must be conceded that a very important link in the diag-

nostic chain of esophageal disease is the esophagoscope. With this instrument we can immediately, with perhaps but rare exception, render a definite opinion as to the nature of the lesion under investigation. Fluoroscopy and x-ray are equally important in the study of all obstructive lesions, and should not be omitted. I would reiterate that esophagoscopy when performed by qualified endoscopists is harmless. Earlier recourse to esophagoscopy in these cases of obstruction might enable us to save patients with early carcinoma by timely surgery.

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CLINIC OF DR. GEORGE G. ORNSTEIN

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IMPORTANT FACTORS REGARDING THE RECOGNITION OF BREATH SOUNDS

FROM the time Laennec introduced auscultation there has been very little departure from the methods of teaching the recognition of normal and pathologic breath sounds heard over the lungs. Emphasis has been placed on memorizing the sounds heard, and any effort made by the student to familiarize himself with the detailed description of the sounds beforehand was frowned upon. It is the custom in medicine to follow the footsteps of our predecessors, and since they taught auscultation in the above manner, it seems we have continued to do so. For many years the training received in auscultation by medical students can best be told by quoting Latham: "The sounds can only be learned by the practice of listening to them. It is useless to describe them. They are simple perceptions of sense which no words can make plainer than they are when the ear has become familiar with them. I must leave you to be your own self-instructors and recommend you to constantly practice auscultation for the purpose." In the course in physical diagnosis breath sounds were perhaps touched on with many other findings during a two-hour period, and from that time on the student was left to acquire as best he could these most important physical findings. Following such training one may become familiar with the important breath sounds, but only after years of experience. I can well remember being told not to be dis-

couraged because of mistakes made and that it generally takes a number of years to become familiar with the signs produced by the lungs.

The work of such men as Louis, Jackson, Walsh, and Flint did no more than record in text-books the description of the sounds. Jackson, an American, working with Louis in Paris, was the first to take notice of the expiratory phase of respiration. Before this observation no attention was given to expiration, and the recognition of the sounds was based entirely on inspiration. Flint has been the greatest contributor to the knowledge of auscultation since Laennec. He realized the importance of describing the breath sounds so that the students could identify the sounds they heard.

In the last few years we have departed from the path of our older teachers and found we could do in a few weeks what required years of experience to accomplish. First, the mechanism of the production of the sound was explained to the student. We then made sure that the student knew thoroughly the description of each breath sound. In the following pages we will attempt to demonstrate the method used.

THE PRODUCTION OF NORMAL BREATH SOUNDS

The act of breathing produces sounds which may be heard over the chest wall called breath sounds. There has been a great deal of discussion as to the origin of these sounds. It was at first thought—as the name “vesicular” implies—that the sound was caused by the entry of air into the alveoli. This view was soon opposed, and Beau¹ in 1834 attempted to prove that all the sounds heard originated in the upper air passages. The glottis was considered as the situation of the origin of this sound. Here the rapid to-and-fro movement of air through a small aperture into a larger tube produced a sound. This laryngeal sound was heard over the trachea and could be traced down the larger divisions of the bronchi. Further investigations of other workers brought forth a conception of a combination of two sources of origin of breath sounds. They believed there was not only a laryngeal but also a vesicular element. The vesicular

element occurred only during inspiration, and the expiration was considered entirely laryngeal. The basis for this conception of a vesicular element was considered on the following experimental work.

Bondet and Chauveau² experimented with a horse afflicted with pneumonia. The pneumonic patch involved the lower half of the left lung. Over this area bronchial breathing was heard on auscultation. Over the remaining part of the left lung and over the right lung exaggerated normal breathing was heard. The trachea was then opened by an incision 20 cm. in length. Following this incision into the trachea (when the wound was kept wide open) on auscultation over the trachea below the incision, the inspiratory murmur was almost lost and the expiratory murmur but faintly heard. Over the consolidated part of the left lung breath sounds were almost absent except for a faint sound during expiration. Over the rest of the lung normal respiratory sounds were heard.

Sahl³ found in a case of pulmonary hernia, due to a sternal fissure, that characteristic vesicular breathing could be heard over the hernia during the performance of a valsalva experiment in which all the laryngeal and glottic sounds were eliminated, and proving that at least a part of the vesicular sound originated in the vesicles themselves.

From the above data it has been accepted that the origin of the sound is both in the larynx and the alveoli.

Bushnell⁴ has recently published his investigation concerning the origin of the breath sounds. He refused to accept any vesicular element. He assumed that both the inspiratory and the expiratory phases of the sound are produced in the larynx, and the sound was dependent upon the vibration of the soft parts of the glottis. His conclusions were based on the following investigation with himself as the subject: After considerable practice he was able to breathe without vibrating his vocal cords. With a laryngologist observing his larynx and an internist auscultating his throat, he breathed with and without vibrating his vocal cords, and it was found that sounds were heard only when there was a vibration of the cords. These workers then

concluded that there was no vesicular element in the production of the sounds.

Myerson and I tried to corroborate the work of Bushnell. We thought that if a bronchoscope was inserted into the trachea the soft parts of the glottis would be entirely eliminated. This form of an experiment would be more certain than the control of one's vocal cords, which was a difficult feat, and, even if observed through a laryngeal mirror, it was difficult for the examiner to say with surety whether there was any vibration. And, then, the question of whether the movements of the cords during inspiration (when the cords are widely separated) and expiration (when the cords are approximated) produced a sound. We doubt whether this movement could ever be eliminated.

During the bronchoscopic examination of one of my patients by Dr. M. C. Myerson we carried out the following investigation: A bronchoscope wide enough to eliminate any movement of the vocal cords and soft tissue of the larynx was inserted into the trachea. Auscultation of the lungs demonstrated that all the breath sounds were heard better than during the examination previous to the bronchoscopy. With the larynx completely eliminated breath sounds were heard with still greater intensity. This investigation not only disproved Bushnell's work but also eliminated the laryngeal element in the production of breath sounds. It is our opinion that the production is similar to that of the production of sound in a pipe organ. The sound being produced as the column of air moves from a large lumen to a narrow one during inspiration and vice versa during expiration.

The next topic to be considered is how the sounds heard over the tracheobronchial tree, termed "bronchial breathing," are changed when heard over the thoracic wall. The sound heard over the trachea is completely changed when heard over the chest wall. This alteration of the sound has never been satisfactorily explained. If one could insert a stethoscope over any of the bronchi a high-pitched sound would be heard similar to that heard over the trachea and perhaps higher in pitch because of the narrower lumen of the bronchi. This same sound when heard over the thorax has both a different pitch and a different quality.

There have been a few explanations of this phenomenon which have not been satisfactory. The one most mentioned in textbooks on physical diagnosis is the one given by Montgomery: "Changes in pitch and quality, although explicable to some extent in the elimination of the weaker vibrations as the whole sound becomes more feeble, appear to be due chiefly to the factors of resonance and interference affecting certain vibrations, while exerting little or no influence on others which go to form the complex group which we term a single sound." The above explanation is not satisfactory. Bushnell has a much better explanation of this phenomenon. The air containing alveoli are compared to a resonator* of fundamentally low pitch. The sounds produced in the tubes consist of a combination of high- and low-pitched tones. The air resonator functioning as a fundamental low-pitch resonator damps out the high- and amplifies the low-pitched tones. He further states that within this resonator there is another one made up of bronchial tubes; this latter resonator has a fundamentally high-pitched tone.

In other words, there are two resonating systems present: a small high-pitched one within a larger low-pitched one. He contrasts the air containing low-pitched resonator as a means of insulation against the high-pitched tones. We cannot agree with this part of the theory. Bushnell assumes the sounds arise in the larynx, which we have demonstrated is not correct. If the sounds did originate in the larynx the resonating system composed of the bronchial tubes should damp out the low-pitched sounds, which then could never reach the alveoli to be amplified. Our impression is that the sounds originate in the trachea and bronchial tree and are dependent entirely on the passage of air from a wide to a narrow tube, and vice versa. The noise produced consists of high- and low-pitched tones. While the former are damped, the latter are amplified by the alveoli acting as a

* If a tuning-fork is placed in a resonator having the same fundamental pitch, the sounds produced by the fork are amplified. If, however, this same tuning-fork is placed in a resonator with a different fundamental pitch, the sounds are damped.

low-pitched resonator. This amplification we call vesicular breathing (Fig. 125).

This resonator theory, if correct, offers us a definite means of interpreting our findings. We must assume that all modifications of breath sounds can only be produced by changes in the

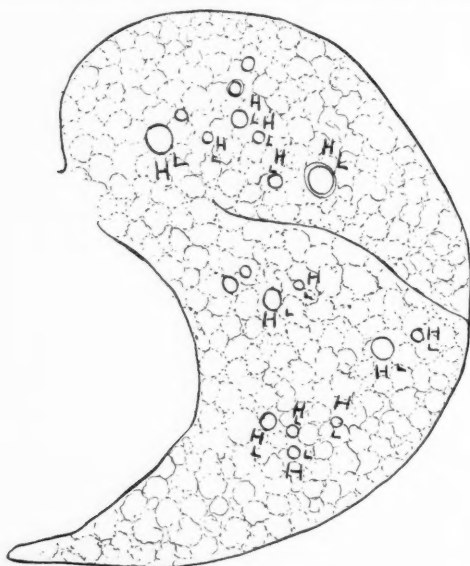


Fig. 125.—This is a diagrammatic cross-section of a lobe of a lung. The bronchi are seen surrounded by aerated lung tissue. In the bronchi noises are produced by the air passing to and fro during inspiration and expiration. The noise is produced by the air column moving from a large tube into a smaller one or vice versa. The noise consists of high- and low-pitched tones. The high tones are damped out by the alveoli acting as a low-pitched resonator, while the low-pitched ones are amplified and heard over the thoracic wall as a sound which we have termed vesicular breathing. *H*, High-pitched tones produced in the bronchi. *L*, Low-pitched tones produced in the bronchi.

air cells which interfere with and modify the low fundamental pitch of the alveoli. Changes in the tracheobronchial tree cannot modify the breath sounds, but can only affect the intensity of the sounds. I have tried to demonstrate the above impression in Fig. 126. It can readily be seen that when there is a modi-

fication of the normal breath sounds pathology must be present in the air-containing alveoli. Pathology in the bronchi does not

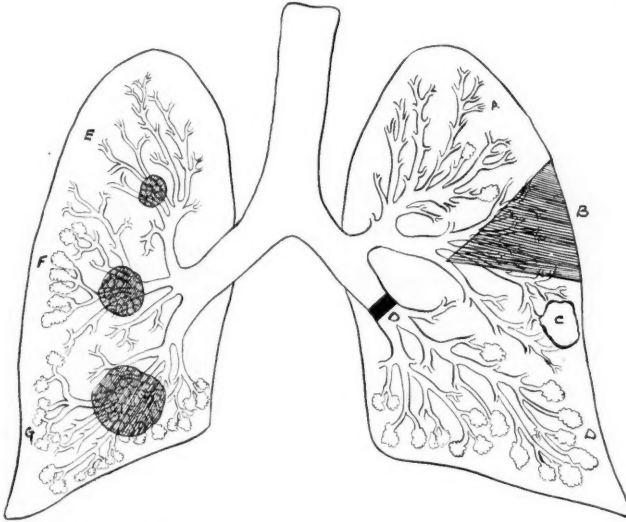


Fig. 126.—*A*, The alveoli acting as a low-pitched resonator damps out the high-pitched tones and amplifies the low-pitched tones. Vesicular breathing is heard over this area. *B*, The low-pitched resonator is changed to one which will amplify the high-pitched tones of the bronchial tubes. Bronchial breathing is heard over this area. *C*, There is another change made in the resonator by cavity formation. Over this cavity cavernous breathing is heard. *D*, *D*, The block of a bronchus changes the intensity of the sound, but does not modify it. *E*, *F*, *G*, Various forms of bronchovesicular breathing.

modify the breath sounds, but only diminishes the intensity of the sound.

BREATH SOUNDS

It is difficult to describe a perception of sense and especially the hearing of sounds. There is no need of describing the rhythmic musical sounds, which have distinctive qualities that allow immediate identification. One would be in trouble in even describing the sound produced by the piano, but could not fail in again identifying it regardless of intensity or pitch. This characteristic quality is not present in the non-rhythmic sounds

heard over the thorax, and though the qualities can be differentiated they closely resemble one another. This will be borne out by the following: In our hospital service it has been the practice to review physical diagnosis with the new crop of interns. Though fresh from courses in physical diagnosis, only occasionally have we had a correct answer for the description of the qualities of inspiration and expiration of vesicular breathing. Though this sound has two different qualities, to the student they sound alike. We therefore must have something more dependable than the qualities of the sounds. And following the teachings of Flint, we have chosen "pitch" as the important factor for differentiation of sounds. And, as a further aid, the hearing of the sound in relation to the beginning and ending of the respiratory movements in inspiration and expiration. The sound heard is divided into phases of inspiration and expiration. During each phase the quality, pitch, and duration is noted, and a comparison made between the two phases. Intensity is of little assistance in the identification of the sound, as will be demonstrated in the following description of the normal and pathologic breath sounds.

NORMAL VESICULAR BREATHING

During Inspiration.—The quality is compared to the murmur heard when the wind softly rustles through the leaves of the trees. This quality has been termed "vesicular." The sound is heard at the beginning and lasts through the phase of inspiration. The pitch is low compared to the sounds heard over the trachea.

During Expiration.—The vesicular quality of inspiration changes to a blowing sound similar to the noise produced when one blows softly with the mouth open. This sound is of the same quality as heard in cavernous breathing and is the cause of the confusion which so often takes place in mistaking vesicular for cavernous, especially when the intensity of the former is exaggerated, as in vicarious emphysematous breathing. The pitch is much lower than the pitch of inspiration. The sound commences with, but only remains for, the first quarter of the act of

expiration. In forced breathing it remains for a longer period. The duration of the expiratory sound varies in different individuals. In some subjects it may be present through more than half of the act of expiration. Students have acquired an im-

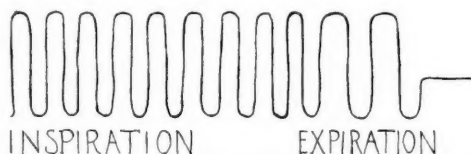


Fig. 127.—A diagrammatic reproduction of vesicular breathing. The character of the wave is the quality; the frequency of the work, the pitch; and the amplitude of the work, the intensity.

pression that the expiratory phase of the sound is frequently absent; this has not been our experience; it is rarely absent.

We have tried to diagrammatically reproduce vesicular breathing (Fig. 127). We note that we have a continuous sound

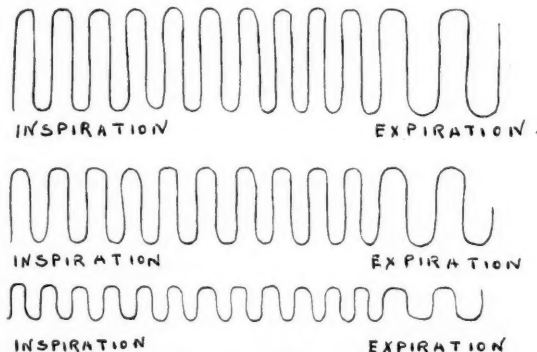


Fig. 128.—Vesicular breathing is diagrammatically reproduced. The intensity varies, but the other characteristics by which the sound is recognized are not altered. Intensity plays no part in the recognition of the sound.

with two distinct qualities, the pitch lowering during expiration. It is also to be noted that the intensity of inspiration is greater than expiration. However, intensity plays no rôle in the recognition of the sounds, as is demonstrated in Fig. 128.

BRONCHIAL BREATHING

During Inspiration.—The quality of this sound is similar to the sound produced by the passage of air through a tube and is termed “tubular” or “bronchial.” The sound is heard with the beginning of the act of inspiration and comes to an abrupt end before the completion of the act. The pitch of the sound is very high.

During Expiration.—The quality is similar to that heard in inspiration. The pitch is much higher. The duration of the sound is prolonged. It starts with and extends through the act of expiration. The intensity is frequently greater than in inspiration.

The sound may be diagrammatically reproduced as in Fig. 129.

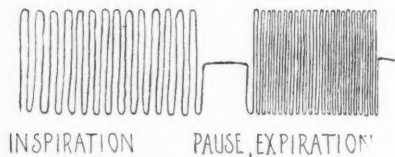


Fig. 129.—A diagrammatic reproduction of bronchial breathing. Quality is demonstrated by the character of the wave, pitch by the frequency of the wave, and intensity by the amplitude of the wave.

Bronchial breathing differs from vesicular breathing in having a distinct pause between inspiration and expiration. The pitch throughout is higher and the reverse occurs in regard to the differences in pitch between inspiration and expiration, the latter now being higher than the former.

CAVERNOUS AND AMPHORIC BREATH SOUNDS

Cavernous and amphoric breath sounds should be considered alike only in the mechanism of their production. These sounds are produced by the air passing through a bronchus, resonated by a cavity. Vibrations set up in the tube over the cavity start sympathetic vibrations within the cavity, which then act as a resonator modifying the original sound. Depending upon the size of the communication to and the elasticity of the

walls of the cavity, one hears amphoric (small sized communication with cavity having solid walls) or cavernous (large sized communication with cavity having elastic walls) breathing. These sounds are not alike, the amphoric sound being musical, while the cavernous is unrhythmic. Amphoric breathing resembles closely a musical tone with a quality impossible to describe. An impression of it may be acquired by blowing over a flask with a very narrow neck. The pitch of this musical sound is usually very high, depending entirely upon the size of the opening entering the cavity. There is little difference in the sound during inspiration and expiration. It is best described as a musical sound of high pitch. It is heard over large non-elastic wall cavities and open pneumothoraces. Over a cavity amphoric breathing is limited to a small area, while over an open pneumothorax it is heard over most of one side of the thoracic wall.

Cavernous Breathing.—During inspiration the quality is of a blowing character similar to the quality of the expiration of vesicular breathing. The pitch, though higher than vesicular, is a great deal lower than bronchial. The duration of the sound varies, always beginning with but frequently ending abruptly before the end of the act of inspiration.

During Expiration.—The quality is the same as during inspiration. The pitch is much lower than inspiration. The duration of the sound again varies, always starting with the act, but frequently lasting through the act.







Cavernous breathing is very easily confused with vesicular breathing (Flint), especially when the latter is exaggerated. The confusion is caused by the similarity of the quality and the pitch of both vesicular and cavernous breathing during expiration. The prolonged blowing, low-pitched expiration of vesicular breathing has been frequently called cavernous breathing. This confusion can be averted by remembering that the qualities of vesicular breathing are different during the two phases of breathing, while the qualities of cavernous breathing are similar. Cavernous breathing is accompanied by a low-pitched pectoriloquy which is absent during vesicular breathing.

With the exception of amphoric breathing, which is readily

recognized by its musical quality, the following rules will help in the recognition of the breath sounds: "When the pitch of expiration is lower than that of inspiration the sound is either vesicular or cavernous breathing. When the pitch of expiration is higher than inspiration the sound is bronchial." (See Chart 1.)

CHART #1.

BREATH SOUNDS.

	<u>VESICULAR.</u>	<u>BRONCHIAL.</u>	<u>CAVERNOUS.</u>
Act of Inspiration.			
Quality Vesicular		Tubular	Blowing
Pitch Low ++		High +++++	Low ++
Duration			
Act of Expiration.			
Quality Blowing		Tubular	Blowing
Pitch Lower +		Higher ++++++	Lower +
Duration			

Degree of pitch expressed diagrammatically in pluses.

The vertical lines represent the beginning and ending of the phases of inspiration and expiration. The horizontal line the duration of the sound.

Before taking up the combination of sounds it is perhaps best to again review the mechanism of the production of the breath sounds. Our belief is that noises consisting of both high- and low-pitched tones are produced by the rushing of air through the bronchial tree; the noise being produced by a similar mechanism as the sound produced in a pipe organ (the passage of air from a large to a narrow tube, and vice versa). It is also our belief that the air-containing tissue acts as a resonator which has a low fundamental pitch. This resonating system damps

out the high-pitched tones, and, at the same time, amplifies the low-pitched sounds which we hear over the thoracic wall as vesicular breathing. Therefore, when there is any interference with this air resonator, higher pitched sounds may be allowed through, as in Fig. 126, *B*.

When there is an infiltration in the parenchyma of the lung the low pitch of the resonator is interfered with. The new medium through which the sound must pass may have a periodicity of that of the higher pitch tones and allow them to pass through to the thoracic wall. When there is a complete infiltration, bronchial breathing is heard. With incomplete infiltration a combination of sounds are heard which Flint called bronchovesicular breathing. This bronchial breathing varies from a minimal (almost vesicular breathing) to almost a complete infiltration (bronchial breathing). The sound, therefore, varies a great deal and is totally dependent upon the amount of infiltration and normal aerated tissue present. While there is no difficulty in recognizing the large amounts of infiltration (almost pure bronchial breathing) it is with the small amount of infiltration that the difficulty of recognition is encountered. If one could pick up these small areas of infiltration which only slightly modify the breath sounds the chest would become a simple problem. How shall we go about it? Let us take a small area of infiltration as in Fig. 126. Two sounds are heard, vesicular and bronchial, with the former predominating. The vesicular breathing is modified as follows: There is a combination of qualities heard which are of little help when one thinks of the difficulty in differentiating the qualities when heard separately. The shortening of the duration of the sound during inspiration and the increase during expiration is of little value. The pitch of inspiration is increased both during inspiration and expiration in the manner shown in Chart 2. To the two plus of vesicular breathing (during inspiration) a plus is added (bronchial breathing is four plus), and to the one plus of expiration, two pluses are added (bronchial breathing is six plus). The pitch of expiration now becomes equal in pitch to that of inspiration, and as the bronchial element predominates, the

pitch of expiration increases. Unless the pitch of expiration is equal to or higher than inspiration, we are not dealing with bronchovesicular breathing.

Bronchovesicular breathing is heard normally over the right upper lobe because of the proximity of the trachea to the right upper lobe. The closer the trachea lies to the right upper lobe, the greater is the area over which bronchovesicular breathing

CHART #2.

	Vesicular Breathing.		Minimal Amount of Broncho- vesicular Breathing.	
INSPIRATION.	Quality	Vesicular	Vesicular and Tubular	
	Pitch	+ +	+ + +	
	Duration	————	————	
EXPIRATION.	Quality	Blowing.	Blowing and Tubular	
	Pitch	+	+ + +	
	Duration	————	————	

Unless the pitch of expiration is equal to or higher than inspiration, we are not dealing with broncho-vesicular breathing.

is heard. It varies in extent in different individuals, and is usually heard from the apex to the second rib anteriorly and to the third vertebral spine posteriorly. Frequently it may be heard as far down as the third or fourth ribs anteriorly and to the fifth or sixth vertebral spine posteriorly. Because of the large amount of air tissue between the trachea and the axilla vesicular breathing is heard in this latter area.

At times it is difficult to interpret bronchovesicular breathing in a right upper lobe. The question arises as to whether we are

dealing with a normal or pathologic condition. Such an occurrence may take place in a tuberculous infiltration in the right upper lobe where the only physical finding is bronchovesicular breathing. We suggest that if a patient comes to you with a history pointing to disease of the lungs, and bronchovesicular breathing is heard in the right upper lobe, do not consider it normal until it is proved so, which can readily be done with the x-ray.

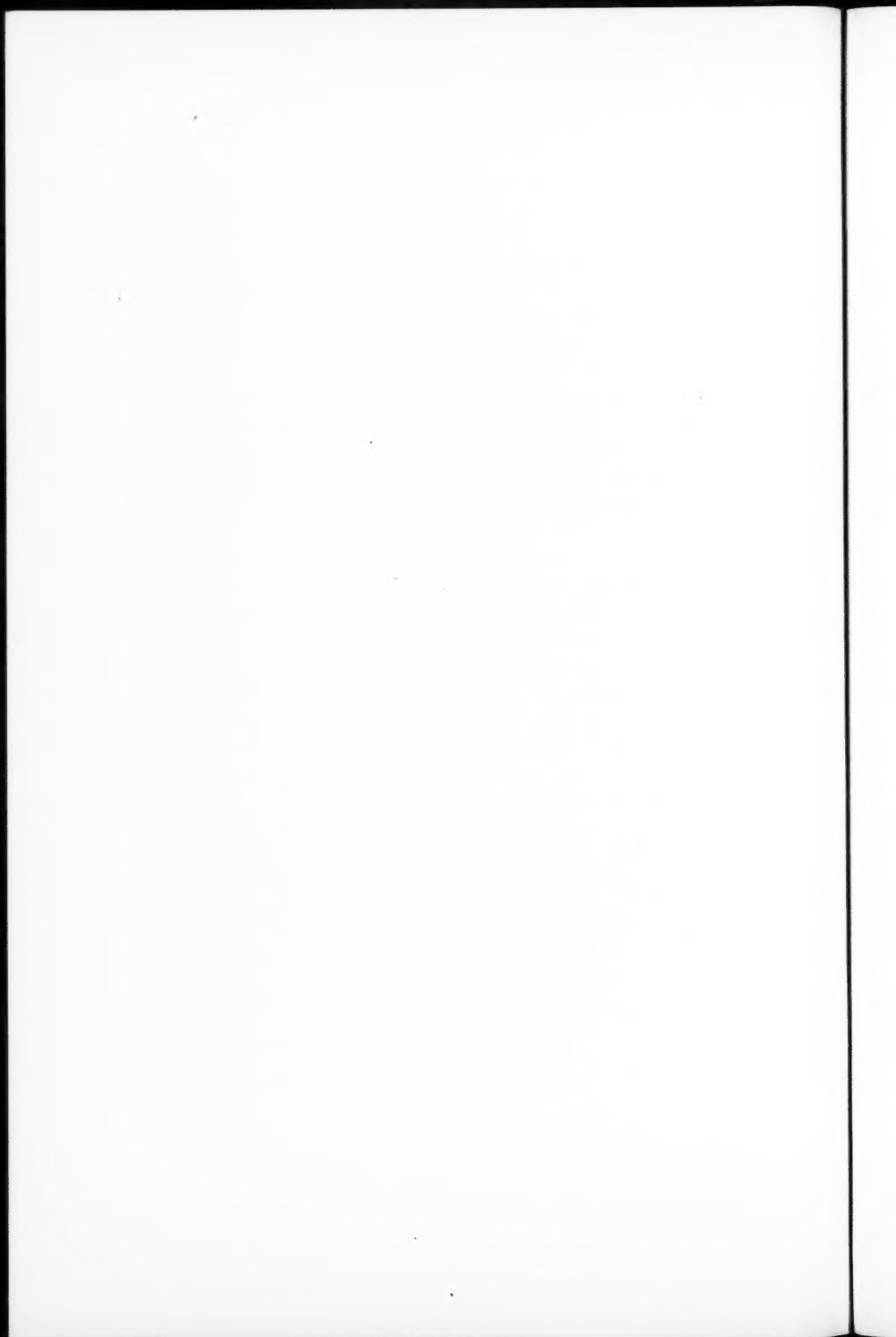
We may also suggest that bronchovesicular breathing heard in the apex of the axilla should always be considered as pathologic. The hearing of vesicular breathing in the axilla, however, does not rule out pathology in the right upper lobe. In a similar manner we may have combinations of bronchial and cavernous breathing.

It is never wise to depend on one characteristic of a sound for its recognition. We urge the student to try to recognize the quality, the pitch, and the duration of the sound during both phases of respiration. If there is to be only one finding to depend on, then, by all means, use *pitch*.

The following rule is of great help in identifying the breath sounds: When the pitch of expiration is lower than inspiration, vesicular and cavernous breathing are to be differentiated. When the pitch of expiration is equal to or higher than inspiration, the sound is either bronchovesicular or bronchial.

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CLINIC OF DR. JESSE G. M. BULLOWA

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CASE I. TRAUMATIC PNEUMONIA; CONTRACOUPE INVOLVEMENT; BACTEREMIA. TREATMENT WITH FELTON'S ANTIBODY SOLUTION. RECOVERY¹

J. S., aged twenty-one, a negro from the British West Indies, was admitted to Harlem Hospital on May 16, 1926. While working in the new subway on May 10, 1926 he fell 22 feet into an excavation, striking his right side. He lay unconscious for about twenty minutes, then he revived, and was able to go home.

There were abrasions over the right forearm, thigh and leg, and a small laceration above his right eye which had been sutured. Since the fall his sputum was bloody. He was up and about until May 14th, when he had a chill, which was followed by a rise in temperature, and soon there was cough with rusty expectoration, shortness of breath, and pain in the left chest.

Physical examination revealed consolidation of the left lower lobe posteriorly. He was very dyspneic. Fluoroscopy revealed radio-opacity of the left lower field with increased radiolucence immediately above the liver.

On admission his temperature was 102° F.; pulse, 114; respirations, 26. The sputum showed Type I pneumococcus by the mouse method. White blood-cells, 6600; polymorphonuclears, 76 per cent.; lymphocytes, 24 per cent.

On admission, pending the typing of the sputum, he was given 5 mls. each of Felton's pneumococcus antibody solution, Types I and II, each mil containing 200 units. One unit is sufficient to protect a mouse from 1,000,000 fatal doses of a virulent culture. Subsequently, whenever the temperature was 102° F.

¹ The cases of pneumonia were studied under the Lucius N. Littauer Pneumonia Fund of New York University.

or over, he received 20 mils. of Type I serum intravenously, with the exception of the third dose; then his temperature had risen to 103.6° F. and his blood-culture, taken twenty-four hours earlier, was found to contain pneumococci. This dose was 30 mils. or 6000 units. In all he received 19,000 units of Type I serum and 1000 units of Type II. There was no reaction from the first two doses of serum. After the 30-mil. dose he had a chill and his temperature rose to 105° F. There was a brief chill after the third dose.

A second and third blood-culture taken on the fourth and fifth days of his illness were negative. The blood-pressure ranged from 112/70 to 90/48. On the eighth day his temperature was normal and he left at his own request on the twelfth day.

The radiograph confirmed the clinical diagnosis of pneumonia involving the left lower lobe.

The result of the treatment with antibody solution was gratifying, for the patient was extremely ill with a positive blood-culture, but the main interest in this case was the onset of bloody sputum immediately after the accident and the subsequent development of lobar pneumonia on the contralateral side. In this patient the blow to the chest was of great force, as indicated by the height from which he fell, the stupor, and the other injuries. In spite of this he was at first not thought ill enough to be put to bed. The development of pneumonia in the other lung was doubtless due to the contracoup or violent concussion of the upper or left lung against its containing chest wall when the right side was suddenly arrested as the patient struck the ground.

In my opinion this man's illness was caused by the accident, notwithstanding the infectious nature of lobar pneumonia, and was subject to compensation under the Workman's Compensation Laws of New York State. A local lowering of resistance to infection is brought about by violent injury as of a blow or prolonged chilling as is so frequently seen in the summer pneumonias which occur in patients who fall asleep under an electric fan or an open window. In this case there is every reason to believe that there was a laceration of the lung.

CASE II. TRAUMATIC PNEUMONIA; TYPE IV PNEUMOCOCCUS; NECROSIS OF LUNG—BRONCHOSCOPY. RECOVERY OF TYPE III PNEUMOCOCCUS FROM SPUTUM. INJECTION OF TYPE III ANTIBODY SOLUTION AND LIPIODOL—RECOVERY

J. A., a structural steel worker, thirty-eight years of age, born in Sweden, was admitted to Harlem Hospital on May 16, 1926. He had been ill three days with chill, fever, cough, dyspnea, and pain in the right chest. The onset had been sudden, with chill and fever. The sputum was blood tinged, and later rusty. He was very weak and prostrated. There was consolidation of the right upper, middle, and lower lobes. There was marked general cyanosis. The tongue was dry and coated. Temperature, 102.6° F.; pulse, 114; respirations, 48. White blood-cells, 23,000; polymorphonuclears, 86 per cent.; lymphocytes, 14 per cent.

This patient narrated that on March 9th, about six weeks prior to the onset of the illness, he had fallen from the first floor of a building, where he was working, to the ground, a distance of 20 feet, striking the right side of his chest and causing contusions of his right arm and legs as well as a laceration of his face. He had been unable to work since the accident on account of weakness and a wound on his leg.

His blood-culture, taken on admission, was sterile. His sputum showed Group IV pneumococci. Temperature rose to 103.6° F. the next day and reached normal on the fifth day, and the pulse slowed to 84, yet there was marked tachypnea (42). The blood-pressure was 80/40 and there was marked loss of tissue turgor. The tongue was dry. The following three days the temperature continued about 100° F. and the respirations slowed to 24 with general improvement until the morning of the tenth day. During and after the tenth day his temperature rose to 102° F., and during that night reached 105° F., with complaint

of pain in the left chest, dyspnea, and acceleration of the respiration to 40. The pulse paralleled the temperature. On this day there was resolution in the right chest and dulness, diminished breathing, and crepitant râles over the left lower lobe. Later in the day there was bronchophony and the next day the patient spat blood frequently.

The temperature fluctuated between 103° and 104° F. for four days, and then gradually fell to normal, and later ranged between 101° and 103.6° F. for a week. The patient was extremely weak and prostrated. He received 3 mls. of digalen intravenously in an emergency, and oxygen. The sputum typed Group IV. On May 30th, the thirteenth day of his illness, the sputum became foul smelling and was grayish black, tenacious, and nummular.

There was amphoric breathing with cracked-pot resonance over the right lower lobe posteriorly. The radiograph revealed a definite fluid level which changed in the lateral recumbent position. The prostration was marked. The blood-pressure 80/36, white blood-cells 14,000, polymorphonuclears 78 per cent., lymphocytes 22 per cent.

On June 4th, the twenty-third day of his illness, he was transfused with 500 mls. of blood. After the transfusion his red blood-count was raised to 3,500,000, hemoglobin to 65 per cent. His sputum was lighter in color and slightly less offensive. There was a definite typical stratification of the collected stinking sputum into three layers. The temperature rose three days later to 105° F. and then fell to 100.5° F. and ranged between that and 102° F. for ten days. On the thirty-fourth day posttussive suction was noted over the angle of the right scapula. The sputum did not show elastic tissue.

Four blood-cultures, taken with each severe accession of temperature, remained sterile. The patient was assisted to suspend himself over the side of the bed several times daily in an effort to empty the lung through posture.

The patient was bronchoscoped by Dr. Mervin C. Myerson. Fluid was aspirated from the right lower bronchus which was found to be inflamed. About 2 c.c. of grayish stinking fluid containing flocculi was collected. The cavity was washed with

sterile saline and finally injected with lipiodol and the patient fluoroscoped and radiographed. The right lower bronchus was well filled in all its bifurcations. There were numerous small dilatations in the region of the terminal bronchioli, some of them in the posterior lappet of the lung below the level of the dia-

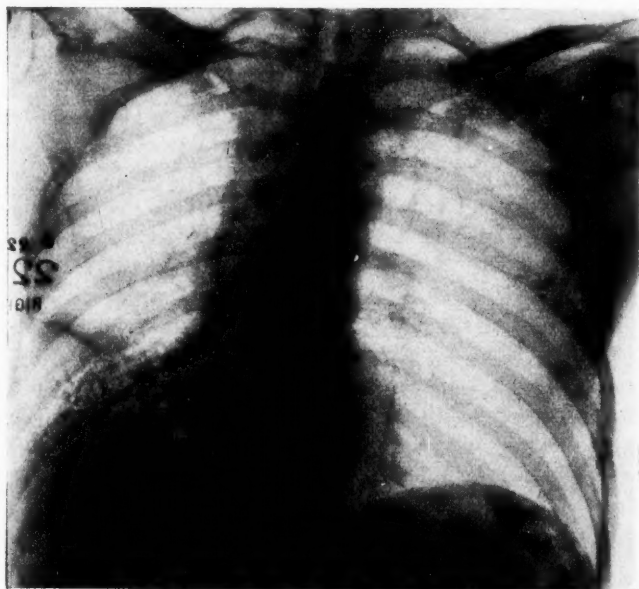


Fig. 130.—The right lower bronchus is well filled in all its bifurcations. There are numerous small dilatations in the region of the terminal bronchioli, some of them in the posterior lappet of the lung below the level of the diaphragm dome. There is no large pocket or accumulation of the contrast substance. The small patch of clouding above the injected area is a remnant of the pneumonic process.

phragm dome. There was no large pocket or accumulation of the contrast substance. This may account for the fortunate outcome without remaining cavity. The small patch of clouding above the injected area is a remnant of the pneumonic process (Fig. 130). The gray flecks proved to be shreds of lung tissue with alveoli and elastic tissue.

A Group III pneumococcus was recovered from the aspirated secretion. The sputum diminished in amount to about half, or to 6 ounces in twenty-four hours.

In view of the specific type of pneumococcus it was decided to attempt therapy locally by injecting antibody solution into the cavity. This was done by Dr. Myerson through a bronchoscope. He washed the cavity first with sterile saline and then with 40 mls. pneumococcus Type III antibody solution.

Following this bronchoscopy the temperature rose to 104° F. for a single day and then remained 101° F. or less for two days, fluctuating between 104° and 101.6° F. for four days without marked change in the physical signs.

The sputum collected after this treatment did not show fluid Type III pneumococcus. It was more fluid, inoffensive, and less in amount.

For another fortnight the patient's temperature ranged between 99° and 101° F., occasionally reaching 102° F. Bed rest on the open-air porch with postural drainage had been continued. Alpine light was administered. Still the sputum continued to have a sweetish sickening odor, and was fairly constant at about 4 ounces a day.

The patient was permitted finally to be up and about on the sixty-fourth day of his illness, although his temperature was not yet persistently normal. Though no spirocheta had been demonstrated, he was given 0.6 mg. of neosalvarsan intravenously. On the seventy-fifth day of his illness he was sent to the Convalescent Home of the Burke Foundation, where he remained thirty-four days. There he gained rapidly in flesh and strength and lost his sputum completely. Five months after the onset the lungs are now clear of râles. There is normal resonance over the right lower chest, but diminished breathing. There are no zones of hyperalgesia referable to the lungs.

This narration presents many interesting points for discussion. Though more than a month had elapsed since the original injury, one must concede that the very great force of the blow to the chest and the constant illness before the onset of the pneumonia make it probable that the accident was a proxi-

mate cause in the ultimate invasion of the lung. The poor resistance of the right lung with subsequent destruction may well be linked with the trauma. In view of the fact that the patient was still under treatment it is a nice question to determine the liability of the carrier under the compensation laws.

If this patient had acquired typhoid during his illness it would be manifestly unfair to attribute the infection to the injury. If his injury had been to an extremity only, without proof that the invasion by the pneumococcus had been through the wound, one could well have rejected as unreasonable the contention of causal relationship. With a direct and severe trauma to the chest with immediate hemoptysis, pain in the chest or expectoration, and subsequent involvement of the side struck, one can well maintain that the accident was the proximate localizing cause of the disease. Glancing blows to the chest without abrasion or immediate sickness are frequently unfairly invoked to account for subsequent hemorrhage or spread of pulmonary tuberculosis.

The occurrence of Group III pneumococcus in the lung cavity and its disappearance from the sputum after therapy is noteworthy. Several years ago the writer reported a lung abscess containing a Group I pneumococcus healed after a single bronchoscopy and infection of the homologous serum by Dr. Imperatori.

Of course, when a number of therapeutic procedures are resorted to in a desperately ill patient, it is, at times, difficult to evaluate the effect of each or any. In this instance the marked local and general reaction resulting from the second bronchoscopy, with a change in the character of the sputum, seems more than a coincidence, though may have been due to the resultant local reaction. The experience should be repeated when the opportunity offers, as it offers a mode of attack for a situation which is frequently tragic in its termination.

In the other or Type I case there was no febrile reaction and immediate prompt recovery.

Notwithstanding the different strains of pneumococci involved, the two cases of pneumonia described are interesting from

the standpoint of their common traumatic etiology. Both occurred as the result of violent blows to the chest without damage to the ribs or external marks of violence on the chest wall.

That pneumonia should follow a penetrating injury of the chest with lacerations and fractures of the ribs is to be expected and is a common experience of surgeons dealing with chest traumata. It is less commonly recognized as a sequel to blows of this nature, without apparent injury to the thorax or overlying skin. Rupture of the azygos veins has been described from concussion of the chest. Külbs has experimented with dogs, striking them on the chest and crushing the thorax, without, however, breaking the bones. He found lacerations, exudations, and hemorrhages into the lung tissue not only at the site of injury, but even in the opposite lung.

Whether the site of injury acts as a point of lessened resistance for an invading organism through the blood-stream, or whether it interferes with the normal mechanism of pulmonary drainage by occluding the bronchioli, or whether the disturbances in the normal mechanism of deglutition leads to an aspiration infection are questions which requires further clinical observation and experimental study.

These cases of chest trauma with resulting pneumonia are not in the same category as the cases of alleged invasion or extension of pulmonary tuberculosis as the result of slight jars to the chest unassociated with violent emptying of the lungs and resultant disturbance of rhythmic breathing.

CASE III. PROBABLE TRANSDERMAL INFECTION WITH SCARLATINA, TYPE III LOBAR PNEUMONIA, AND STAPHYLOCOCCUS AUREUS ABSCESS—RECOVERY

M. S., an Irish ironworker, aged twenty-seven, was admitted to Harlem Hospital on March 28, 1926. He entered the hospital complaining of pain over his left shoulder, axilla, and both left axillary folds. A liniment applied had aggravated the pain which was also aggravated by cough or movement of his arm. He had had fever, headache, and a cough. There had been chilly sensations, but no severe chill. Three days prior to the onset, or six days before coming to the hospital, there were chilly sensations while at work. He had had rheumatism three years before. The patient, a very well-nourished and muscular man, appeared extremely ill and complained of cough, fever, and pain in the chest, and he was raising rusty sputum. The tongue was heavily coated and moist. The tonsils were large and red. There was no angina typical of scarlatina. The skin of the left chest was abraded; elsewhere the skin was clear. Over the right lower chest there was marked dulness and over the left, impaired resonance. At the left base there were moist râles and squeaks. Over the right base there was diminished breathing with a small patch of bronchovesicular breathing, and increased spoken and whispered voice above the angle of the right scapula.

There was tenderness and swelling of the left posterior axillary fold. Next morning there were definite signs of consolidation in both lower lobes and the cellulitis of the axilla was more extensive. The sputum was Group III by the mouse method. No serum was administered to this patient, as he had been ill more than four days with his pneumonia and our specific serum was being reserved for the earlier cases.

The next day, the fifth day of his illness, the blood-count was 13,500 and 16,200, polymorphonuclears 91 per cent. The tem-

perature continued to range between 102° and 103.4° F., the pulse was relatively slower, usually about 100, respirations 26 to 30.

On the sixth day of his illness there was a generalized maculopapular erythematous rash on the abdomen, chest, shoulders, and extensor surface of the extremities. There was no angina. With the outbreak of the rash there was an acceleration of the pulse to 120.

In view of the scarlatinal character of the rash, 30 mls. of scarlatina antitoxin was administered intravenously and 20 mls. intramuscularly into the buttock. The surgeon, Dr. Friedman, concurred in the diagnosis of cellulitis of the left axilla and counselled drainage under local anesthesia.

In view of the persistent high temperature scarlet fever serum was administered twice the next day. The rash faded and the temperature reached 100.2° F. on the twelfth day, where it fluctuated for several days. The rash subsided and the local redness and swelling about the axilla diminished markedly after the administration of the serum. Several futile attempts were made to find a collection of pus in the axillary fold.

The consolidation of the right lower lobe which had been found on physical examination and radiographically confirmed, gradually resolved. Though induration and redness had diminished, there was deep tenderness over the axillary fold and the temperature continued.

Five days after the first dose of serum a serum rash and polyarthralgia appeared and the temperature commenced to climb, reaching 104.8° F. three days later. At this time thick creamy pus was found in the axillary fold and drained under local anesthesia. This pus showed *Streptococcus hemolyticus* and was sent to Dr. Anna Williams, of the Research Laboratory of the Department of Health, who found it to be a scarlatinal strain by means of toxin serum neutralization experiments.

Temperature continued to oscillate between 101° and 104° F. for a week, and although the signs of sacculated fluid in an area below the angle of the right scapula developed, no fluid was found on several aspirations. The temperature gradually subsided, with ultimate complete recovery. During the long confinement

in bed the patient developed a large abscess of the buttock which yielded a *Staphylococcus aureus* from the pus. An intern, who dressed the chest wound, developed an angina and a typical scarlatina eruption; he had had no other known exposure.

This case is particularly interesting in view of the complications of a dual infection, pneumococcus Type III, scarlatina *Streptococcus hemolyticus*, with ultimately a third organism, *Staphylococcus aureus*. It is noteworthy that in our series of several hundred typed cases of pneumonia we have thrice recovered a Group III pneumococcus in cases complicated by the pyococci. One was a *Staphylococcus aureus* infection of a superficially lacerated finger with invasion of the blood-stream by that organism and a pneumococcus Type III pneumonia. This patient recovered after a stormy course, losing the finger and having several metastatic foci. In one culture there were 100 colonies per mil.

The other, an infection of the arm, after phlebotomy in a fatal illuminating gas poisoning. This woman had a Type III pneumonia and later a *Staphylococcus aureus* in the blood-stream as determined by four cultures. It is impossible to say whether this is merely a coincidence. The question as to which condition is primary is a fruitful source for speculation only.

The route of invasion of the scarlatina streptococcus in this case must continue debatable. It is impossible to determine whether it was a throat infection with chance localization in the axilla, or one determined by a slight trauma, or whether it was a skin infection as the result of an abrasion. Certainly the prodromal symptoms, pain in the axillary fold and chilly sensations, and late onset of the rash maximal about the cellulitis, suggest the latter course of invasion. An x-ray showed no necrosis of any rib on the left side. Even the finding of scarlatinal streptococci in the throat would not have been decisive, as the patient might well have been a carrier. The prompt response of the rash and the local redness and infiltration to the antiscarlatinal serum in the presence of a localized infection suggest that some of the so-called postoperative or other surgical erythemata are actually rashes due to scarlatinal strains of streptococci. In

this case the strain was determined and the therapeutic result was clear cut, disposing of such controversy.

The use of the scarlatinal serum was probably life saving. Though the blood-stream showed no organisms, this patient was greatly poisoned by the products of the localized streptococci which seemed to be made less virulent until the onset of the serum sickness, when there was apparently an increase of local destruction and then pus was found and evacuated. At this time it is probable that there was still sufficient antitoxin in the blood to neutralize the toxin and protect the skin and distant organs.

If there had been less careful bacteriologic study of the sputum the clinical course might have been interpreted as an unusual and early invasion of the lung in a generalized streptococcus infection. The correct explanation for the sequence of events affecting this patient is apparently the one offered as probable; it is supported by the fact that the blood-cultures remained sterile.

CASE IV. TYPHOID FEVER WITH CHILLS, FEVER, AND SWEATS. TYPHOID ABSCESS IN THE RECTUS ABDOMINIS SHEATH. TYPHOID PULMONARY INVOLVEMENT. RECOVERY

A YOUNG white woman, stenographer, aged twenty-three years, was brought to Harlem Hospital on January 2, 1926. She complained of headache, fever, and abdominal distress which had lasted three weeks. She narrated that three weeks prior to her admission to the hospital while riding in a subway train she had had a headache and a fainting spell. Upon recovery she went home suffering from the headache, discomfort in the epigastrium, and nausea. She continued at work for a week, then she began to have fever, especially in the evening, with occasional chills lasting a few minutes, and occasional night-sweats. Her bowels did not move normally and since the onset she was drowsy. The intern recorded that while taking the history the patient was dull, apathetic, and listless. Her pupils reacted normally and she complained of photophobia. There was some clotted blood in the nostril; there were two petechial spots on the chest; the lungs were normal; the abdomen was lax; the spleen was not felt; the knee-jerks were absent; the patient was much emaciated.

Next day the knee-jerks were noted as present and there was an ankle-clonus and Kernig on the left side.

The Widal was negative. The spinal fluid was bloody in all specimens. The white blood-cells were 2800; polymorphonuclears, 60 per cent.; lymphocytes, 40 per cent.; temperature 103° F.; pulse, 100; red blood-cells, 2,600,000; hemoglobin, 60 per cent. The urine showed a trace of albumin. A blood-culture was negative.

In view of the marked lethargy, the petechiæ and the inconstant nervous symptoms, and an occasional systolic blow at the apex tentative diagnoses of encephalitis lethargica or bacterial endocarditis were made.

Dr. Blakeslee, the neurologist, found the pupils irregular in outline, the left possibly greater than the right. The extended arm showed slight drooping of the left hand. Facial weakness was present on the right side. The tongue deviated to the left. There was a hyperactive Achilles' jerk on the right side, with permanent clonus, and a slightly diminished left Achilles. There were active and equal knee-jerks; questionable bilateral Babinski, and a left Oppenheim more active than the right. The abdominal reflexes were more active on the left than the right. There was no nuchal rigidity, yet a mild bilateral Kernig. He concluded that there was an acute infection overwhelming the central nervous system or an acute encephalitis.

The ear drums were negative; the blood-culture continued negative. The lymphocytes were counted repeatedly, the greatest white blood-count was 5800; polymorphonuclears continued about 60 per cent. The blood-pressure continued low (110/70). The urine showed a trace of albumin and occasional red and white blood-cells. The temperature ranged between 103° and 104° F. and pulse about 120 for the first three days in the hospital, then the temperature fell to 102° F. and the pulse to 110. The spleen was not felt.

On the sixth day after admission the patient had a chill lasting twenty minutes, and the temperature rose to 104.4° F. The blood-count continued low, with 60 per cent. polynuclears. On several occasions the white blood-cells were less than 3000 even after the chill. The temperature oscillated 2 degrees, gradually descending each morning, and ranged from 104° to 100° F. Blood-smears were bare of plasmodia. Though repeated Widal's were negative, a specimen of stool, taken on January 8th, the sixth day in the hospital, showed *Bacillus typhosus*. The Widal continued negative until the fourteenth day in hospital. A second blood-culture remained negative. The patient then continued to run a higher temperature, on the eighth and ninth days almost 104° F. Finally, on the tenth day, the temperature reached 105° F. and for the following week it ranged from 98.4° to 105° F. every day or every other day. The temperature was low during the nights, but reached 105° F. in the early morning hours, frequently with chilly sensations, and fell with a severe sweat.

On the sixteenth day of residence, the highest temperatures commenced to be lower and gradually, in steps of $\frac{1}{10}$ or $\frac{2}{10}$ of a degree, fell to 101° F. on the twenty-fourth day. It still continued to oscillate between 98.4° and 102° F. until the twenty-sixth day, when it gradually reached normal.

On the fourteenth day some sibilant and sonorous râles were noted over the left apex anteriorly and Roentgen examination of chest showed a clouding of the lateral aspect of the upper portion of the left pulmonary field. The apex of the lung itself was quite clear, there were no strands running from the hilum.

On the twenty-eighth day some tenderness of the abdomen above the pubis was noted in routine examination. Gradually a mass appeared in the suprapubic region about 3 by 2 inches. It could be moved laterally from side to side and seemed to be under the sheath of the left rectus muscle. By this time the temperature had reached 99° F. for an entire day, but the pulse, which had never been slow and always disproportionately rapid with each accession of temperature and each recurring daily chill, continued rapid, between 110° and 120° F.

The mass was aspirated; living typhoid bacteria were obtained from the thin grayish pus. Under local anesthesia it was drained. It was deep in the muscle sheath. The surgeon could not trace the mass to the pubis. No bare bone could be felt.

The patient was carefully nursed and, from the beginning, careful count was kept of the calories taken. They were gradually increased from 950 to 3500 and even more, and the patient finally left the hospital in excellent nutrition on the fifty-sixth day after her admission.

In this case the salient features are the marked involvement of the nervous system at the onset, the late appearance of the Widal, the extreme leukopenia, and the occurrence of a septic type of temperature, with later discovery of an abscess in a rectus muscle.

The diagnosis of typhoid fever may have appeared to be obvious with a developing spleen and the appearance of the Widal in the presence of a typhoid bacillus infected intestine. However, the daily chills, the sweats, and the very rapid pulse with

the physical signs in the upper portion of one lung made it a matter of much difficulty to exclude malaria, pulmonary tuberculosis, and bacterial endocarditis. The older clinicians would have called this type of fever "typhomalarial." Plasmodia were diligently searched for in the blood, and the sputum was often examined for tubercle bacilli without avail. Several blood-cultures were made; these were sterile. The persistent low blood-count was against a pyococcal infection. The localization in the abdominal muscle may have been an accidental occurrence attendant upon a blood infection. Such chance invasions of the bones or the muscles of the back explain typhoid spine. The fact that the surgeon could not feel bare pubic bone does not exclude a periosteal origin of the abscess, though the direction in which the abscess pointed lends support to the view that it was primarily a muscle rather than a bone invasion. It is possible that Zenker necrosis of the muscle was responsible for the site of the localization, being, as it was, a point of lessened resistance; this is true especially in the presence of the nausea or the coughing with abdominal muscle strain. The writer has seen such a destruction of muscle with abscess formation several times during the grippe epidemic of 1918. In some the abscess occurred in the upper portion of the belly of the recti; in such cases it was limited by the inscriptions. The abscess, which ultimately became as large as a man's fist, was never contaminated by pyococci, and the reaction induced by pyococci in the blood was persistently absent.

The pulmonary involvement was probably a typhoid pneumonia. Clinically it could not be differentiated from tuberculosis by physical signs. The radiograph was entirely different from tuberculosis and more like a patch of lobar pneumonia.

It is quite probable that the sputum in this case might have been shown to contain *Bacillus typhosus* if suitable methods of culture had been employed.

It will prove interesting to determine whether a pneumococcus infection could stimulate a leukocytosis in the presence of an active typhoid invasion.

**CASE V. SELF-INDUCED AVITAMINOSIS. BERIBERI
AND SCURVY. MEDICOLEGAL ASPECTS. PERIOD
FOR DEVELOPMENT AND FOR CURE**

P. K., an Irishman, aged fifty-five, a hotel porter, was first seen at the request of the insurance carrier. Two and a half weeks previously he had tripped while at work, and falling, had struck his right knee and thigh. He thought he must have injured his left wrist because, since the accident, it had become weak. He was able to walk home—over a mile and a half—but in a few days his thigh began to swell and he limped. Progressively he became weaker and was soon unable to be about. For several days he had been bleeding from his gums and was now unable to turn in bed without distress in his leg and marked palpitation and shortness of breath.

I found him in his dark, tenement home, quite weak, waxen white in color, with his face puffy about the eyes. There was no conjunctivitis, though there was photophobia. The gums were enormously swollen and bleeding; they looked like blood-wursts on either side of the teeth. The teeth were in poor alignment. There was poor occlusion and, in fact, mandibular protrusion. The pulse was 112, temperature 99.6° F., respirations 24. There were râles at the bases of the lungs. The veins of the neck pulsated.

The heart sounds were of poor quality and there was a systolic murmur over the base. The blood-pressure was 124/76. The radials and bronchials were thickened and tortuous. The liver was slightly enlarged; the spleen was not felt.

The skin of the thighs and forearms was covered with a macular hemorrhagic rash which in several places was confluent. There was swelling of the tissues of the legs with ready pitting. The lower portion of the left thigh was tender and much larger than the left. The tenderness and induration was deep and evidently involved the lower end of the right femur, so that a green-

stick fracture with callous formation could only be excluded by radiograph. The knee-joint was normal. The reflexes were diminished. There were no sensory disturbances of the lower extremities. The left grip was much weaker than the right. The left extended wrist drooped. There was wasting of the interossei in the left hand and the wrist-jerk was diminished. There were no constant sensory disturbances, though the patient's attention was not held.

The patient narrated that for four and a half months he had lived on tea and bread. He had "taken a disgust" for meat, which he could not now chew because of his painful jaws. He had taken no fruit or vegetables, as he could not bite into them and because he thought oranges beyond his means. For several months he had been slightly short of breath, but he had accepted the condition without seeking medical advice.

It was quite obvious that the patient was suffering from a self-imposed avitaminosis. He had deprived himself of the water-soluble vitamin, responsible for nerve degeneration or beriberi, and of the antiscorbutic vitamin.

After five days he was taken into Flower Hospital. His urine was yellow, acid, specific gravity 1020, with a faint trace of albumin. His hemoglobin was 45 per cent.; red blood-cells, 2,526,000; white blood-cells, 2500; polynuclears, 42 per cent.; eosinophils, 1 per cent.; large lymphocytes, 4 per cent.; small lymphocytes, 53 per cent. The Wassermann was negative. The temperature fluctuated between 98° and 100° F., respirations 20.

The radiograph taken then showed no fracture of wrist or femur. It revealed very marked arterial calcifications. There was no other bone pathology.

This patient was placed on a diet consisting of kidney stew, the juice of 6 oranges a day, and whole wheat porridge or rolled oats twice daily at first; later, on a full ward diet as well as the oranges and whole wheat bread, the symptoms disappeared. He was also given cod-liver oil, though there were no symptoms of rickets. Though at first he had to be lifted even in bed, in twelve days he was discharged well. Three weeks later he was quite hearty, his teeth were firm, and the gums healed.

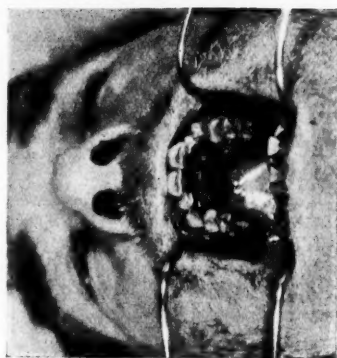


Fig. 131.—Note spongy gums of scurvy. When first seen the hemorrhagic masses were like two blood sausages along the teeth and almost obliterated a view of the palate which has a very high arch. There is swelling of the lower portion of the right thigh with evidence of the faded petechial rash. The scaling skin testifies to the previously more tensely swollen leg. The left wrist-drop with atrophic interosset are evident.

The fall in this case probably was the immediate cause of the periosteal hemorrhage, and, as such, was compensatable under the laws of New York State, because it aggravated the symptoms of an existing disease; but it would have been unfair, in my opinion, to have charged this man's death to injury had he succumbed, because the subperiosteal hemorrhage merely produced aggravated local symptoms, but did not accelerate the progress of his disease. William C. Archer, a learned referee of the New York State Department of Labor, holds that industry should be required only "to restore the injured workman to the *status quo ante* in the case of episodes induced by trauma such as hemorrhage, or failure of cardiac compensation, which may be recurrent when they occur in the course of a chronic disease."

The patient is a typical instance of what was formerly known as "ship beriberi," which is a combination of the deprivation of the antineuritic vitamin, first described by Eijkman, and the antiscorbutic vitamin.

The four and a half months required for the development of the disease is a brief period. Infants rarely develop scurvy in less than six months unless they are premature. If the hemorrhage induced by trauma had been in the brain then, it might have been a cause of death and probably compensatable.

The extra metabolism attendant on work hastens the metabolic exhaustion of the vitamin. In beleaguered cities scurvy occurs in the garrison earlier than in the inhabitants. The prompt recovery in three weeks is interesting. Park has found that any single method of treatment cures rickets in that time. In our case improvement was evident in two days.

The marked improvement in the gums without local attention lends support to the view held by many physicians that pyorrhea is conditioned to a large extent by unrecognized dietary deficiencies.

CLINIC OF DR. S. EDWARD KING

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THE DIURETIC ACTION OF UREA AND HIGH PROTEIN DIETS

INTRODUCTION

UREA is the most wide-spread nitrogenous substance in animal tissues, representing the major end-product of protein catabolism. Its primary function in the human economy is to provide an inert and extremely soluble form of nitrogen elimination. Its main channel of excretion is through the urine, where it constitutes about 85 per cent. of the urinary nitrogen.^{1, 2}

W. Friedrich³ was the first to use urea as a diuretic in 1892. He employed doses of from 2 to 14 gm. daily in cardiac edema and in cirrhosis of the liver with ascites, reporting favorable results. In 1895 Klemperer⁵ reported relief of ascites of hepatic origin with daily doses of 10 to 20 gm. In 1896 Strauss⁶ reported diuresis and clinical improvement in cases of ascites and of pleural effusion with urea in similar doses. In 1915 Friedrich⁴ used 2 to 14 gm. in renal dropsy with some success. The use of urea up to this time remained largely limited to cases of edema and effusions of extrarenal origin.⁷

It remained for Volhard⁸ in 1918 to employ doses of 40 to 60 gm. daily in renal dropsy. His results were very good and he emphasized its value in cases of nephrosis.

Employing these large doses Feichenfeld⁹ in 1918 reported remarkable results in various types of edema and ascites. He extended its use to cases of edema with associated renal sclerosis. When renal impairment was absent, he employed doses up to 100 gm. daily. He cites a case of nephrosis with massive edema

which had failed to respond to thyroid, caffeine, diuretin, and theocin orally, and to theophyllin and ephyllin intravenously. Following urea in doses of from 20 to 100 gm. daily the edema completely disappeared. No untoward symptoms occurred except thirst. In 3 of his cases of cardiac edema without renal impairment, urea completely reduced the edema after digitalis and other diuretics had failed. Diuresis also occurred after urea in 2 out of 3 cases of cardiac edema with renal sclerosis. He confirmed Volhard's observations as to the efficacy of urea in nephrosis, and concluded that its use was not necessarily contraindicated in other types of renal dropsy provided nitrogen retention was absent.

In 1919 Schon¹⁰ studied the effect of urea administration on the N. P. N. of the blood. No rise occurred in 3 cases with initial N. P. N. values of from 50 to 60 mg., after 100 gm. of urea daily for periods up to five months. Diuresis appeared in all these cases. He concluded from these observations that moderate initial elevations in the blood-nitrogen were no contraindications to the use of urea.

Strauss¹¹ in 1921 summarized the subject and included in his report some cases of Feichenfeld's. In a series of 7 cases of nephrosis, diuresis followed urea in all but 1 case. He cites 1 case which had received a total of 12 kilograms of urea in six months, with only beneficial results. Good results were also obtained in other types of renal dropsy. In 12 cases of cardiac edema with associated renal sclerosis, urea succeeded where digitalis, theocin, and novasurol had failed. Increased urinary volume with disappearance of fluid from various sites followed the use of urea in cirrhosis of the liver, polyserositis, and pleural effusions.

H. McLean¹² in 1921 recommended the use of urea in doses of 30 gm. daily in renal dropsy, particularly in nephrosis.

Because of the prevalent conception of the toxicity of urea^{13, 14} these observations failed to gain recognition in this country. When employed at all, the small doses precluded any material results. Its use finally fell completely into discard. The value of urea as a diuretic in cardiac edema was again emphasized in

1925 by Crawford and McIntosh.¹⁵ They gave up to 60 gm. daily in 8 cases, producing complete disappearance of the edema in 7.

DISCUSSION

The diuretic action of urea is obtained through the stimulus exerted by an elevated urea content of the blood. In accordance with the mathematical laws of Ambard, McLean,¹⁶ Van Slyke,¹⁷ and others¹⁸ the rate of urea excretion depends largely on the blood-urea concentration.

Crystalloids, such as urea, when excreted by the kidneys carry with them corresponding amounts of fluid. When their maximal urinary concentrations are attained, further elimination is accomplished by increased urinary volume. Normally there exists a direct relationship between the urinary volume and the urea content of the blood and urine.

Members of the purine group of diuretics and the mercurials, such as novasurol, are essentially renal irritants. Their use is not free of danger. Hematuria, transient anuria, and general systemic reactions, such as headache and gastro-intestinal disturbances, often follow the use of such drugs. Similar symptoms together with salivation and hemorrhagic colitis have been noted with even minute doses of novasurol (0.2 c.c.). Undoubtedly these diuretics produce considerable though transient renal injury.

Urea ordinarily is not a renal irritant. It is constantly excreted by the kidneys in large amounts. Doses of 100 gm. daily over periods up to six months have been reported¹¹ without evidence of renal irritation. Leiter,¹³ after injecting over 1 per cent. of the body weight of urea intravenously in dogs, could demonstrate only fatty degeneration and cloudy swelling in the tubules, whereas hemorrhages were present in the brain and intestinal tract. These hemorrhages were probably due to the marked osmotic pressure changes produced by injection of large amounts of urea.

Urea is an effectual and fairly dependable diuretic in doses of 45 to 60 grams daily, which may be continued for periods of weeks or even months. If kidney function is not impaired, the

dose may be increased to 100 grams daily. Large doses may be employed in ascites of mechanical origin due to abdominal malignancy, or hepatic cirrhosis, in congestive heart failure, polyserositis, and nephrosis. In other types of edema associated with renal impairment it may be employed in smaller doses, 15 to 45 grams daily. In the latter cases undue blood elevations should be avoided by frequent estimations of the blood-urea. It is safest to discontinue the drug, temporarily at least, when blood-urea N concentrations exceeding 100 mg. are attained.

The maximum amount that can be taken at one dose without producing gastric disturbance is 20 grams. It is best administered in a freshly prepared concentrated aqueous solution. The disagreeable metallic taste may be disguised by addition of flavoring agents, such as tincture of orange or lemon. Coffee and tea are recommended by Strauss¹¹ as excellent vehicles. For convenience it may be prepared in powders which are dissolved in water prior to ingestion. Only freshly prepared solutions should be used because of the decomposition of urea in solution. The best time of administration is shortly after meals.

Rectal administration was ineffectual in our experience. This was previously noted by Strauss.¹¹ Diarrhea may follow its use.

Untoward symptoms occasionally develop during urea therapy. They are either gastric or systemic in character. The former, consisting of nausea and vomiting, are referable to the metallic, acrid taste of urea. They usually occur at the very onset of administration in susceptible individuals, and disappear when the medication is stopped. Systemic toxic symptoms, such as headache, dizziness, and torpor, were described by Hewlett, Gilbert, and Wickett¹⁴ after rapid ingestion of 100 gm. of urea. They considered 160 to 245 mg. or over as the toxic zone of blood-urea, but higher values are frequently encountered in chronic nephritis without symptoms. The rapidity of accumulation in the blood rather than the eventual concentration appears to be the determining factor in the appearance of these symptoms. High blood-urea concentrations when rapidly produced are often followed by severe gastro-intestinal disturbances, particularly vomiting and diarrhea. The re-excretion of consider-

able quantities of urea into the gastro-intestinal tract under these conditions, as demonstrated by Leiter,¹³ is the probable cause of these symptoms. Severe thirst is an occasional symptom following urea administration.

Although failures with urea occur for no obvious reason, usually they are attributable to two main causes. The first is insufficient absorption from the gastro-intestinal tract due to vomiting; the second is due to insufficient response by functionally impaired kidneys.

Diuretic response follows urea therapy in some cases of chronic nephritis with initially elevated blood-urea. This follows from the fact that increased blood-urea concentrations do not necessarily indicate a complete inability of the kidneys to excrete urea. According to McLean¹⁶ these cases eliminate as much urea daily as the normal, for otherwise progressive retention would follow. The rise in blood-urea acts as a diuretic, though it requires a distinctly higher level than in individuals with normal kidneys.

The rate of urea excretion and consequent diuresis is directly proportional to the functional capacity of the kidneys. The response to urea therapy may be gaged according to the ability of the kidneys to eliminate urea at a normal, slightly impaired, or markedly impaired rate. These results will be taken up individually.

GROUP A. NORMAL RATE OF UREA ELIMINATION

The most satisfactory diuretic results are obtained in cases of edema, ascites, and effusions with kidneys of normal urea excreting capacity. The diuresis is immediate and proportionate to the dosage. No retention of urea occurs in the blood fourteen hours after the last dose.

Case Reports.—The effect of urea administration in cases of edema with kidneys capable of eliminating urea at a normal rate.

Case I.—(See Table I.) A. H., No. 7356, female, age thirty-seven.

History: Marked edema of four months' duration.

Physical Examination: Essentially negative, excepting for

general anasarca. Blood-pressure 132/80. Eye-grounds negative; infected tonsils.

Laboratory Examination:

Blood Chemistry: Serum proteins, 3.74; albumin, 1.28; globulin, 1.46; chlorids, 0.526.

Urine: Specific gravity 1024; moderate to large amounts of protein; many granular casts; no red blood-cells.

Basal Metabolism: 12 per cent. below normal.

Diagnosis: Chronic nephrosis, diseased tonsils.

Hospital Course: Weight fell from 175 to 157 pounds following restriction of fluids and salt; moderate edema still persisted.

Urea Therapy: Following urea administration in doses of 20 to 60 grams daily a moderate diuresis was established, with loss of 9 pounds in eleven days. At the end of that period all edema had disappeared. There was no elevation in the blood-urea as determined fourteen hours after the urea medication was stopped. There were no untoward symptoms.

Summary: A case of nephrosis responded to urea by diuresis without any elevation in blood-urea after digitalis, limitation of fluid, and a salt-free diet had failed to reduce the edema completely.

Case II.—(See Table I.) A. K., female, No. 9409, age seventy.

History: Progressive jaundice, ascites, and edema of four weeks' duration. Epigastric pains, melena, six weeks.

Physical Examination: Jaundice, ascites, moderate edema of lower extremities.

Laboratory Examination:

Blood Chemistry: Urea N, 13.5; CO₂, 43.8 per cent.; chlorid, 0.511.

Urine: Specific gravity 1022; negative for albumin and sugar; microscopic examination negative.

Diagnosis: Carcinoma of gall-bladder, peritoneal carcinomatosis.

Hospital Course: Progressive ascites and edema of legs.

Urea Therapy: Sixty grams of urea given daily for three days produced diuresis with a loss of 10 pounds of weight. Subsequently slight nausea with the general uncomfortable con-

dition of the patient indicated paracentesis. The edema had disappeared. No elevation in blood-urea occurred.

Summary: A case of abdominal malignancy with ascites and edema responded to urea with diuresis and complete reduction of edema. No rise in blood-urea occurred. Gastro-intestinal disturbances that appeared were not attributable to urea.

TABLE I

THE EFFECT OF UREA IN CASES OF EDEMA WITH KIDNEYS CAPABLE OF ELIMINATING UREA AT A NORMAL RATE

The diuresis produced is not accompanied by any residual elevation of the blood urea.

Case.	Date.	Period, days.	Urea dose, gm.	Weight, pounds. ¹	Blood urea N ¹ mg. per 100 c.c.	Fluid c.c. average for total period.			Remarks.
						In-take.	Urine.	Balance.	
I A. H. 7356 F.	November								Nephrosis.
	1st	..	0	157	8.7	1320	800	+520	
	2d	1	20	156	1380	1400	- 20	
	3d	1	30	1230	1450	-220	
	4th	1	60	155	11.7	960	1400	-440	
	5th	2	30	156	925	1250	-325	
	7th	4	45	151	1150	985	+165	
	11th	1	60	150	12.5	1020	1320	-300	
	12th	1	25	149	1000	660	+340	
	13th	148				
II A. K. 9409 F.	January								Abdominal malignancy. Vomited.
	6th	1	0	160	13.5	..	300	
	7th	1	20	158	740	700	+ 40	
	8th	3	60	153	680	1340	-660	
	11th	3	0	148	17.7	610	520	+ 90	
	14th	1	60	840	1400	-560	
	15th	145	800	900	-100	

¹ Figures for blood urea N and weight apply to the first day of each period.

GROUP B. RATE OF UREA ELIMINATION SLIGHTLY IMPAIRED

The initial blood-urea may be normal in these cases. Renal impairment is indicated by the progressive rise in the blood-urea following administration. When discontinued, the blood-urea gradually falls to normal within a week.

Good diuretic results are obtained.

Case Reports.—The effect of urea therapy in cases of edema with slightly impaired urea excretion.

Case I.—(See Table II.) A. H. (readmission).

History: The case of nephrosis previously reported reappeared six months later with identical symptoms.

Hospital Course: Weight was reduced from 161 to 154 pounds by fluid and salt restriction.

Urea Therapy: Urea administered in doses of 45 grams daily for one week and 60 grams daily for three weeks produced a moderate diuresis with the loss of 8 pounds in weight. Only slight residual edema remained. A gradual rise in the blood-urea nitrogen occurred up to 44.3 mg. at the end of the four-week period. This elevation persisted for one week after urea therapy was stopped. Presumably the progressive degenerative lesion had impaired renal function to the extent of producing urea retention which had been absent six months ago following urea therapy.

Summary: A good diuretic response was obtained with urea in a case of nephrosis with slightly impaired ability to excrete urea. Renal impairment was indicated by urea elevation in the blood which persisted for a week after the medication was stopped.

TABLE II

EFFECT OF UREA IN CASES OF EDEMA WITH KIDNEYS WHOSE ABILITY TO EXCRETE UREA IS SLIGHTLY IMPAIRED

The diuresis produced is accompanied by a moderate rise in the blood urea which persists for less than a week.

Case.	Date.	Period, days.	Urea dose, gm.	Weight, pounds. ¹	Blood urea N ¹ mg. per 100 c.c.	Fluid c.c. average for total period.			Remarks.
						In-take.	Urine.	Balance.	
I A. H. readm. F.	March 5th	..	0	780	670	+ 90	Nephrosis.
	8th	7	45	154	10.0	890	1110	-220	
	15th	22	60	152	24.0	878	1120	-242	
	April 9th	1	45	146	44.3	925	1450	-525	
	10th	..	0	146	37.0				
	15th	21.0				
II L. H. 5466 M.	November 9th	..	0	142	10.2	516	510	+ 6	Nephrosis.
	10th	11	60	913	1650	-737	
	21st	3	0	135	56.3	727	530	+197	
	24th	1	20	..	13.5	670	525	+145	
	25th	7	60	138	..	926	1716	-790	
	December 2d	1	0	133	40.8	630	1050	-420	
	3d	1	20	..	15.0	765	750	+ 15	
	4th	1	40	134	..	750	1400	-650	

¹ Figures for blood urea N and weight apply to the first day of each period.

Case II.—The detailed report of Case II is omitted to avoid repetition. (See Table II.) In this case the elevation in the blood-urea, although marked, persisted only for one day. The impairment in urea excretion apparently was less than in Case I. Complete reduction of all residual edema followed urea in this case after theocin, novasurol, and other diuretics failed.

GROUP C. RATE OF UREA ELIMINATION MARKEDLY IMPAIRED

The blood-urea is usually above normal on ordinary diets. After prolonged protein restriction normal levels may be obtained.

Although a diuretic effect from urea is compatible with impaired function, the response differs from those heretofore described. At the onset of urea therapy there is a latent period of several days during which no increase in urinary volume occurs. The blood-urea rises rapidly. At the end of this period diuresis appears and continues as long as urea is given. The level of blood-urea at which diuresis occurs may be considered the elevated renal threshold for these impaired kidneys. The higher pressure of blood-urea enables the kidneys to excrete larger quantities of urea than possible at a lower level.

The elevation in blood-urea persists for two to three weeks after urea has been discontinued. Large doses of urea may produce such rapid accumulation in the blood in these cases as to produce toxic symptoms of headache, restlessness, and gastrointestinal disturbances. Skilful administration of moderate doses controlled by frequent blood-urea determinations may yield good therapeutic results.

In cases functioning maximally without any reserve the additional stimulation by urea produces no diuretic response. A progressive retention of urea in the blood occurs (Case III).

Case Reports.—The effect of urea therapy in cases of edema with urea excretion markedly impaired.

Case I.—(See Table III.) E. L., No. 8934, female, age fifty-one.

History: Diabetes mellitus for twelve years. Marked hypertension for three years. Dyspnea, edema, and ascites of several months' duration.

Physical Examination: Extreme congestive heart failure. Marked anasarca. Marked cardiac hypertrophy and dilatation. Blood-pressure 210/160.

Laboratory Examination:

Blood Chemistry: urea, N 32; uric acid, 5; CO_2 , 39 per cent.

Urine: Specific gravity 1010; faint trace of protein.

Diagnosis: Hypertensive cardiovascular disease. Congestive heart failure. Diabetes mellitus. Chronic nephritis (primary contracted kidney).

Hospital Course: Admitted in extremis. Admission weight could not be taken. Two days later the weight was 188 pounds. Following digitalis and restriction of salt and fluid, weight fell to 167 pounds. Marked residual edema was still present.

Urea Therapy: Urea was given in increasing doses of 35, 45, and 60 grams for six days. No response was obtained until the fourth day, when diuresis appeared. A loss of 5 pounds occurred in the next two days. The blood-urea N, which at the beginning was 18.7, rose to 63 on the fourth day and to 98 two days later. Medication was discontinued because of nausea and headache.

During an interval period of eleven days oliguria reappeared, with gain in weight. The blood-urea N remained elevated at 34.8 mg. Urea was resumed in daily doses of 45 grams for a period of twelve days. The same sequences of events occurred. A latent period of four days, during which time the blood-urea N rose to 53.6 mg., was followed by marked diuresis with daily volumes up to 2400 c.c., as compared to previous volumes of 500 c.c. A loss of 5 pounds in weight followed. The blood-urea N rose progressively to 108, when toxic symptoms of headache, restlessness, nausea, and vomiting appeared.

The specific gravity of the urine which previously had been about 1010, characteristic of contracted kidney, on this admission varied from 1020 to 1028, characteristic of the kidney of chronic passive congestion. During urea diuresis it again fell to 1012 and 1010.

Summary: A case of cardiac decompensation with markedly impaired kidney function responded to urea by a diuresis which

appeared only when the blood-urea N exceeded 60 mg. The progressive retention of urea necessitated its discontinuation when toxic symptoms appeared at blood-urea N concentrations of about 100 mg.

Case II.—A detailed report of Case II, which is similar to Case I (see Table III), is omitted.

Case III.—(See Table III.) E. K., female, No. 7761, age eight years.

History: Hematuria with edema seven weeks previously. Fever and cough one week.

TABLE III

EFFECT OF UREA IN CASES OF EDEMA WITH KIDNEYS WHOSE UREA EXCRETION IS MARKEDLY IMPAIRED

A rapid and immediate rise in the blood follows urea administration. If moderate residual function is present, diuresis may eventually appear at a high threshold (Cases E. L. and M. H.). The elevation in blood urea persists for weeks after urea administration has been discontinued. In kidneys without functional reserve the blood urea rises rapidly without any diuresis (Case E. K.).

Case.	Date.	Period, days.	Urea dose, gm.	Weight, pounds. ¹	Blood urea N ¹ mg. per 100 c.c.	Fluid c.c. average for total period.			Remarks.
						In-take.	Urine.	Balance.	
I E. L. 8934 F.	January 10th	2	0	167	18.0	940	380	+ 560	Cardiac decomp. Contracted kidney.
	12th	1	45	167	18.7	960	425	+ 535	
	13th	1	35	168	1720	1150	+ 570	
	14th	4	60	167	760	1340	- 580	Nausea and vomiting.
	18th	1	20	166	98.0	325	1800	-1475	
	19th	11	0	162	780	665	+ 115	
	30th	1	45	159	34.8	640	500	+ 140	
	31st	1	30	940	700	+ 240	
	February 1st	10	45	159	63.6	1150	1590	- 440	Headache, nausea, vomiting, thirst.
	11th	..	0	156	108.0	795	1400	- 605	
	12th	77.0	
II M. H. 8377 F.	November 25th	2	0	140	11.1	1060	600	+460	Chr. dif. neph.
	27th	3	40	138	920	1050	-130	
	30th	1	20	137	57.5	1000	2000	-1000	Vomited.
	December 1st	1	0	65	93.8	800	450	+ 350	Subacute neph. Contracted kidney. Edema increased.
III E. K. 7761 F.	2d	5	20	625	510	+ 115	
	7th	1	15	68	905	650	+ 255	
	8th	3	30	630	430	+ 200	
	11th	3	20	72	125.0	860	200	+ 660	
	15th	220	

¹ Figures for blood urea N and weight apply to the first day of each period.

Physical Examination: Slight edema. Pallor. Pneumonic consolidation of the left upper lobe. Blood-pressure 110/80. Eye-grounds negative.

Laboratory Examination:

Blood Chemistry: Urea, N 63; uric acid, 10.8; CO₂, 33 per cent.

Urine: Specific gravity at admission 1020; subsequently fell to 1010. Protein in moderate amounts. Many casts and red blood-cells.

Diagnosis: Lobar pneumonia, subacute nephritis.

Hospital Course: The pneumonia resolved in two weeks. The edema gradually increased, with gain in weight from 52 to 65 pounds in three weeks. Ultimate death from uremia.

Urea Therapy: Urea in daily doses of 15 to 30 grams for twelve days was followed by no diuretic response. Increase in weight continued as before. The blood-urea N rose to 125 mg., but there were no toxic symptoms at this time.

Summary: Urea produced no diuretic effect in a case of subacute nephritis showing very marked glomerular involvement at autopsy.

The use of urea was preceded in these cases by a preliminary reduction in weight and edema, accomplished by rest in bed, digitalis, and restriction of salt and fluids. Various diuretics, such as diuretin, theocin, novasurol, and ammonium chlorid, had previously proved unsuccessful. In two cases hematuria had followed small doses of novasurol.

HIGH PROTEIN DIETS

High protein diets frequently exercise a marked diuretic effect in cases of nephritic edema. This observation, made by Epstein,^{16, 17, 18} in cases of nephrosis has been repeatedly confirmed, notably by Allbutt,¹⁹ Symmes,²⁰ and McLean.¹² Epstein's^{18, 21} theory of edema which is based on the work of Starling²² on lymph production, assumes the reduction of the plasma proteins in nephrosis to be the primary cause of the edema. He considers the diuretic action of high protein diets an indirect result of replenishment of the plasma proteins.

Considerable doubt as to the validity of Epstein's hypothesis has been raised recently by Linder, Lundsgard, and Van Slyke.²³ They were unable to find any fixed relationship between the concentration of the plasma proteins and either the extent or course of edema. Our experience has been entirely similar. There appears to be no fixed value or concentration of plasma proteins below which edema appears. Cases with low plasma proteins without edema are encountered.

The immediate diuretic response that follows high protein diets can scarcely be dependent upon a slow process, as resynthesis of amino-acids into plasma proteins.²⁴ A more likely explanation has been advanced by McLean,¹² De Wesslow, and Wordley,²⁵ who consider the diuresis dependent upon the large amounts of urea liberated by high protein diets.

The diuretic mechanism of high protein diets is in all respects similar to that of urea. If the capacity of the kidney to excrete urea is good, diuresis is immediate without any elevation of the blood-urea. The effect is proportionate to the dosage, *i. e.*, of the grams of protein. Where kidney capacity to eliminate urea is seriously impaired, rapid elevation of blood-urea occurs without diuresis. The diuretic effect of these diets is independent of the previous or ultimate plasma protein concentration.

Case Reports.—Case I (see Table IV). A. R., male, No. 10,824, age sixty-one.

History: Edema two weeks, dyspnea three weeks.

Physical Examination: Edema, ascites, hydrothorax, cardiac hypertrophy. Blood-pressure, 170/90. Eye-grounds, retinal arteriosclerosis.

Laboratory Examination:

Blood: Urea N, 40.8 on admission, subsequently fell to 19.9; uric acid, 3.7; CO₂, 52.2 per cent.; serum proteins, 4.12; albumin, 2.36; globulin, 1.76; cholesterol, 230.

Urine: Specific gravity 1020; protein heavy trace; many white blood-cells; occasional casts and red blood-cells.

Diagnosis: Acute diffuse nephritis (glomerular nephritis with nephrotic component, classification of Volhard and Fahr). Arteriosclerosis.

Hospital Course: Admission weight of 233 pounds was reduced to 229 following restriction of fluids and salt and use of digitalis. Theocin twice produced a slight diuresis, but was followed by vomiting. The daily protein intake during this period was between 30 and 45 grams.

High Protein Therapy: Increase of protein in diet to 120 grams daily was immediately followed by a very marked diuresis. The weight fell in eighteen days from 229 to 197 pounds, a loss of 32 pounds. Urinary volume increased from daily averages of about 900 c.c. to over 3600 c.c. The blood-urea N did not become elevated and at the end of this period was 17.1.

Summary: A case of subsiding acute nephritis with good urea eliminating function responded to high protein diet with a marked diuresis and loss of 32 pounds without any elevation in the blood-urea.

Case II (see Table IV). B. G., male, No. 10,062, age eighteen.

History: Recurring attacks of general anasarca fifteen months, duration. Urine occasionally bloody; frequent headaches; blood-pressure reported elevated.

Physical Examination: Edema, ascites, blood-pressure 160/104, diseased tonsils.

Laboratory Examination:

Blood: Urea N, 9.0; sodium chlorid, 495; CO₂, 44.3 per cent.; serum proteins, 5.47; albumin, 3.38; globulin, 2.09.

Urine: Specific gravity fixed at about 1020; large amount of protein; few casts; red blood-cells noted once.

Diagnosis: Chronic diffuse nephritis (glomerular nephritis with nephrotic component, classification of Volhard and Fahr).

Hospital Course: On daily intake of 45 grams of protein average urinary volume was 800 c.c. On 60 grams daily average urinary output increased to 1200 c.c., and on 120 grams daily to over 1500 c.c. A total loss of weight of 15 pounds occurred. The blood-urea N, which was 15.8 initially, was 17.9 at the end of the period.

Summary: A case of chronic diffuse nephritis with good urea excreting function responded to a high protein diet with loss of 15 pounds in weight without any rise in the blood-urea.

Case III (see Table IV). J. A., male, No. 11,789, age twenty-five.

History: Anemia five months, edema and ascites five weeks. Scarlet fever when a child. Nocturia for five weeks. Albuminuria noticed for five years. Hematuria one year ago. Increased blood-pressure previously noted.

Physical Examination: Marked anemia, edema, anasarca, cardiac hypertrophy, aortic insufficiency. Blood-pressure 168/54. Eye-grounds tortuous arteries.

Laboratory Examination:

Blood: Urea N, 17.9; cholesterol, .223; CO₂, 30 per cent.; serum proteins, 3.88; albumin, 2.39; globulin, 1.49.

Urine: Specific gravity constantly about 1012; moderate amount of protein; frequent red blood-cells.

Diagnosis: Chronic diffuse nephritis; aortic regurgitation.

TABLE IV
THE DIURETIC ACTION OF HIGH PROTEIN DIETS

In kidneys capable of excreting urea at a normal rate, high protein diets produce an immediate diuresis without any residual elevation of the blood urea (Cases A. R. and B. G.). When the power of the kidney to excrete urea is seriously impaired (Case J. A.) progressive urea retention occurs without any diuresis.

Case.	Date.	Period, days.	Protein, gm.	Weight, pounds. ¹	Blood urea N ¹ mg. per 100 c.c.	Fluid c.c. average for total period.			Diagnosis.
						In-take.	Urine.	Bal-ance.	
I A. R. 10,824 M.	March 1st	12	40	233	40.8	970	990	- 20	Acute nephritis.
	13th	25	120	229	19.9	1475	2435	-960	
	April 7th	190	17.1				
II B. G. 10,062 M.	February 7th	6	45	155	15.8	960	585	+375	Chronic diffuse nephritis.
	13th	14	60	149	...	1090	1210	-120	
	27th	5	80	143	17.4	1120	1370	-250	
	March 4th	2	120	142	...	1525	1550	- 25	
	6th	140	17.9				
III J. A. 11,789 M.	April 5th	6	30	156	17.9	1350	790	+560	Chronic diffuse nephritis.
	11th	11	150	158	...	1165	715	+450	
	22d	159	62.0	

¹ Figures for blood urea N and weight apply to the first day of each period.

Hospital Course: Edema unchanged, increasing acidosis; death from uremia.

High Protein Therapy: One hundred and fifty grams daily protein intake for eleven days produced no diuresis. The weight remained constant. A progressive retention of urea in the blood occurred, the urea N rising from 17.9 to 62 mg. After the high protein diet was discontinued the blood-urea N continued rising to 106 mg.

Summary: In a case of chronic diffuse nephritis with markedly impaired kidney function, no diuretic effect was produced by high protein diet. A progressive retention of urea in the blood occurred.

SUMMARY

1. Urea is a fairly dependable non-toxic diuretic in doses of 45 to 60 grams daily. It may produce diuresis where other diuretics have failed.

2. Its action is produced without any apparent irritation of the kidneys.

3. In kidneys capable of excreting urea normally the diuresis is immediate and proportionate to the dose. Fourteen hours after the last dose no elevation in the blood-urea is present.

4. In kidneys with defective urea elimination the response is less immediate and retention in the blood occurs in proportion to the extent of renal impairment.

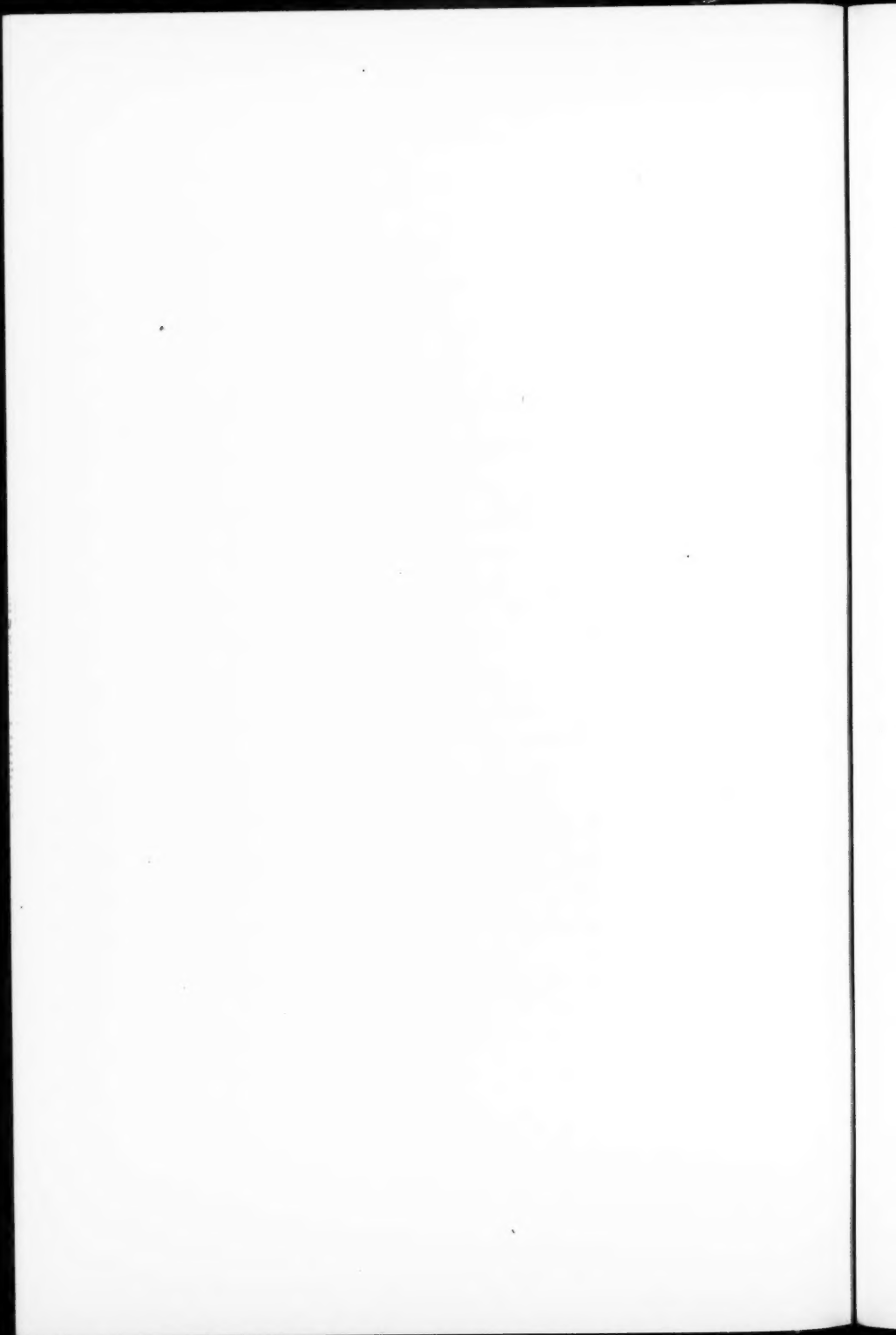
5. Diuretic effects with urea are compatible with initially elevated blood-urea concentrations if sufficient residual kidney function is present.

6. The diuretic action of high protein diets is dependent upon and proportionate to the amount of urea it liberates. Its mechanism is in all respects similar to corresponding amounts of urea given by mouth.

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CLINIC OF DR. RANDAL HOYT

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SPECIAL THERAPEUTIC CONSIDERATIONS IN SYPHILIS OF THE NERVOUS SYSTEM

THE process of recovery following the administration of anti-syphilitic treatment can be divided into the following three stages:

1. Distribution of antisyphilitic drug throughout the body.
2. Sterilization and cessation of pathologic activity.
3. Restitution to normal.

In the so-called "general" syphilis as bodily conditions are such as to facilitate the accomplishment of each of the above steps in the majority of cases, they do not enter into practical consideration. In neurosyphilis, however, adverse conditions obtain which are liable to interrupt the process of recovery.

1. Distribution of Antisyphilitic Drug Throughout the Body.
—Most organs and tissues of the body being profusely vascularized, this process is readily accomplished by the blood-stream. Vascularization of the nervous system, however, is somewhat unique, in that it is supplied only by systems of arteries which are virtually terminal. Thus to quote from Tilney and Riley: "There is no anastomosis between the smallest brain arteries. If one of these is obstructed there is no further possibility of re-establishing the circulation." When such obstruction occurs as the result of a neurosyphilitic process (a frequent occurrence) the lesion automatically cuts itself off from the source of therapy. The treponemata it harbors being then uninfluenced by treatment are free to migrate, in virtue of their motility, into adjacent tissues and extend the disease.

2. Sterilization and Cessation of Pathologic Activity.—Owing to the poor vascularization of the nervous system and the liability of neurosyphilitic processes to become isolated, complete sterilization of this form of syphilis is frequently impossible. In spite of the fact that all the treponemata which invade the nervous system cannot be destroyed, such cases do not necessarily become progressively worse. On the contrary, there are many cases in which partial sterilization is sufficient to bring about the termination of pathologic activity. The re-establishment of a state of latency under such circumstances can be explained only by assuming that the involved nerve tissue still possesses a certain capacity for maintaining its own defense. Thus the end-result of many cases of neurosyphilis depends not upon the type of antisyphilitic treatment administered, but upon how efficiently the nervous system can defend itself against those treponemata which cannot be sterilized.

Consideration of the defense mechanism in neurosyphilis is of the utmost practical importance for two reasons: First, it explains why seemingly similar cases of this disease respond so differently to the same kinds of treatment; second, it emphasizes the importance of including in the therapy of neurosyphilis those procedures which increase the efficiency of the defense mechanism.

3. Restitution to Normal.—After the cessation of pathologic activity in syphilis all cells involved in the preceding reaction return to anatomic and functional normal except those which have been completely destroyed. The latter undergo various forms of cicatrization. Owing to the modern methods of establishing the diagnosis of syphilis while in its early stages, residual cicatrization in the "general" form of syphilis is usually not sufficiently extensive to interfere with the function of the organ in which it occurs. In the nervous system, however, microscopic destruction in certain areas produces wide-spread incapacitating symptoms. On this account it frequently happens in neurosyphilis that although the disease itself has been inactivated, symptoms remain.

Applying the above to the practical management of neuro-

sypilis, it is obviously apparent that the therapist has not only to treat the basic infection but has also in many cases to anticipate or circumvent those obstacles to the process of recovery which so frequently arise.

Thus, first and foremost, he must determine whether the arteries of the nervous system are sufficiently open to convey anti-syphilitics administered by routine treatment to the underlying neurosyphilitic process. This can often be accomplished as follows:

Before any treatment is given subject the patient to a detailed serologic and neurologic examination (recording any neurofunctional abnormalities no matter how trivial or inconsequential they may seem). Then administer routine treatment for about six weeks and re-examine the nervous system. If the original findings have disappeared, the arteries of the nervous system can be regarded as patent, and routine treatment can be continued.

Should neurofunctional abnormalities persist after routine treatment, however, it means either that vascular obstruction (total or partial) has occurred or that the part of the nervous system causing the symptom has been permanently destroyed. A suggestive but not absolute method establishing the differential diagnosis between these two conditions is the correlation of clinical findings and spinal fluid serology. Should a symptom persist, but the spinal fluid change from positive to negative, it is probable that the arteries are open and that the symptom is due to cicatricial formation; on the other hand, should the spinal fluid remain positive, vascular occlusion should be suspected.

Once vascular occlusion has occurred, the question as to the advisability of instituting intraspinal therapy arises. Were we certain that the benefit derived from intraspinal treatment was due solely to the drugs injected into the subarachnoid space, it would be possible to lay down a fixed rule for the employment of this form of therapy, namely, to use it only in cases having superficial neurosyphilitic processes (*e. g.*, in immediate relationship with the subarachnoid space). Such a rule, however, cannot be formulated, because as yet we do not know the effects of spinal

puncture and removal of spinal fluid in themselves. Many cases improve as the result of these procedures alone, and based upon this empirical fact the institution of intraspinal therapy is seemingly obligatory in all cases of neurosyphilis which do not respond to routine treatment.

The support of the defense mechanism in neurosyphilis is not as fanciful as it might seem upon first consideration. It is true we do not understand the biochemical nature of this defense, but there are certain clinical observations which throw a side-light upon influences which both augment and deplete it.

Thus, Moore has observed that symptomatic neurosyphilis is much less frequent in women who have been pregnant than in men, or women who have never been pregnant, and he believes something occurs during pregnancy which protects the nervous system.

That malaria increases the resistance of nerve tissue to the *Treponema pallidum* is now familiar.

Of the depleting influences upon neurodefense, trauma is perhaps the one most commonly observed. An individual having an unsuspected latent neurosyphilitic process receives a minor head injury, and shortly thereafter complains of neurologic symptoms not due to the injury, as he thinks, but to the reactivation of the underlying process. Alcohol, in itself an intoxicant to the nervous system in certain individuals seems, to lower the resistance to the treponema, and in some instances is the precipitating cause of active neurosyphilis, and in others prevents recovery in individuals receiving treatment. Alcohol, therefore, should be prohibited in all cases of syphilis.

At the New York Skin and Cancer Clinic we have observed the frequent coincidence of focal infection in mouth or throat and active neurosyphilis, and have also noted conversely that elimination of these foci frequently increases the efficiency of antisyphilitic treatment. We have also observed active neurosyphilis follow adverse psychogenic influences (*e. g.*, worry, a financial catastrophe, marital difficulties, etc.), and again, conversely, have noted improvement in the efficacy of treatment once these influences were controlled.

To prevent permanent symptomatology in neurosyphilis it is merely necessary to apply to this disease the same rules that are employed in general syphilis, namely, to recognize the disease and institute treatment before extensive permanent destruction has occurred. Thus in "general" syphilis the saddle-nose has become a rarity, not due, however, to improvement of the drugs used in treatment, but to the fact that those intranasal processes which eventually destroy the septum can be recognized and terminated while in their formative stages. In neurosyphilis there are two types of functional disturbances of man, incapacitating or permanent, which systematic methods of procedure ought to prevent. Thus, syphilitic hemiplegia is due, usually, to cerebral endarteritis in general and to endarteritis of the lenticulostriate artery in particular. Until the latter artery is involved the underlying disease does not produce subjective symptoms of any consequence to the patient; to the clinician, however, who is on the lookout for this condition there are revealed many evidences of this disease of an objective nature, and were he to institute treatment while the disease was in this subjective phase incapacitating symptomatology could in many cases be anticipated and prevented.

The tabetic process involves the dorsal columns of the spinal cord. These columns transmit nerve impulses from the muscles, joints, and tendons to various parts of the central nervous system. Their chief function is to aid in the regulation of bodily balance. Incidentally these impulses also reach the cerebral cortex, where they combine and produce that state of consciousness known as the position sense. Individually, however, they seldom pass beyond the threshold of consciousness, and most individuals are unaware of the fact that such a thing as joint, muscle, or tendon sense exists. Therefore when these sensations are impaired as the result of the tabetic process their loss remains unnoticed, and the disease, being unsuspected on that account, continues. Then those impulses which regulate the balance function are impaired, but at first this does not produce any effect because the loss is compensated for by other parts of the nervous system, so that still the disease remains asymp-

tomatic. Finally, however, the disease progresses so far that it produces functional defects for which compensation is no longer possible, and impairment of the balance mechanism or ataxia ensues. So extensive is the destruction at this time, however, that complete recovery under treatment is out of the question.

The same tabetic process can also produce incapacitating symptoms by extension. Thus if the process originally in the dorsal columns were to extend into the vesical center of the cord, incontinence would ensue, and because the disease had advanced extensively in order to cause this symptom the probability of controlling it is unlikely.

Bearing in mind that the tabetic process involves the sensory (or, more properly speaking, afferent) department of the spinal cord, the seemingly obvious procedure to identify it is to examine the sensations. But how often is this done? At the Skin and Cancer Clinic we have corrected this omission and have frequently identified early spinal syphilis while in the formative stages, and have controlled it therapeutically before incapacitating symptomatology has appeared.

The same principles of diagnosis which apply to the early diagnosis of hemiplegia, ataxia, and incontinence apply to other parts of the nervous system, and it is our belief that if more methodical study were employed in the prophylaxis of neurosyphilis such unfortunate conditions as tabes, paresis, paralysis, etc., would become as rare as the saddle-nose.

From the point of view of the neurologist the tendency is seemingly to overemphasize the importance of spinal fluid serology and underemphasize nerve function. For, valuable as the former is, it nevertheless has its interpretative limits, and to endeavor to force its application beyond these limits is merely to endanger throwing into disrepute one of the most valuable tests known to medicine. On the other hand, to belittle the value of neurofunctional examination is an evasion of the fact that when all is said and done neurosyphilis *is* a disease of the central nervous system which structure must be examined methodically for the same reason that the lungs are examined in pulmonary tuberculosis.

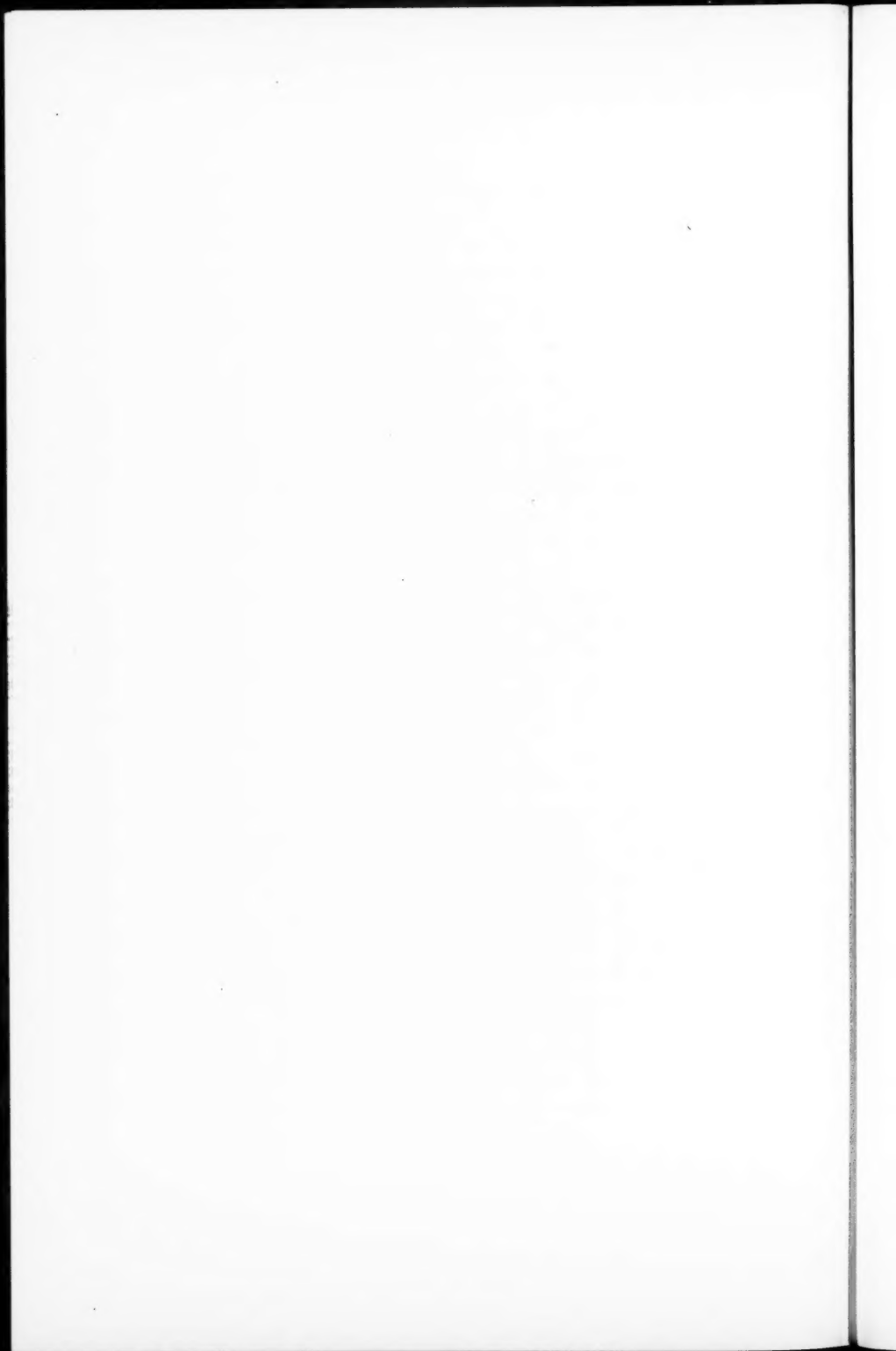
Summary.—The process of recovery following antisypilitic treatment is often interrupted in syphilis of the nervous system. These interruptions are due to occlusion of the terminal arteries of the nervous system, to inadequacy of the neurodefense mechanism, or to the fact destruction of an important part of the nervous system has occurred before treatment has been instituted.

The therapist has always to bear in mind these interruptions are liable to occur in neurosyphilis and should anticipate them or endeavor to circumvent them when they exist.

Arterial obstruction can sometimes be circumvented by intraspinal therapy.

The efficiency defense mechanism of the nervous system can often be augmented by eliminating those influences which deplete it.

Permanent symptomatology can in many instances be prevented by recognition and treatment of the processes causing it while in their formative stages.



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THE TONIC NECK REFLEXES AND THEIR CLINICAL SIGNIFICANCE IN TUBERCULOUS MENINGITIS IN CHILDREN

Introduction.—When the midbrain of an animal (dog or cat) is transected at the level between the anterior and posterior colliculi (corpora quadrigemina) it assumes a rigid posture in which all the limbs become extended and the head is retracted. This posture, which is practically constant, is known as anti-gravitational, and the animal is said to be in a state of decerebrate rigidity. The animal has lost the power (reflexes) of righting itself if overthrown, and always resumes its rigid posture in whatever position it is placed. If, however, the transection is made cephalad to the midbrain and the thalamic connections are left intact, the animal retains the normal power of righting itself, although it still is decerebrate.

Basing his experiments upon those of Sherrington with decerebrate animal preparations, Magnus observed that if the head of such an animal was rotated to one side, the limbs on the side to which the snout was turned became, if possible, more rigid and extended, while those on the opposite side (to which the occiput pointed) became flexed and lost tonus. On reversing the position of the head the limbs previously extended and rigid became flexed and lost tonus, and the limbs previously flexed became extended and rigid. However often he repeated this maneuver the limbs invariably extended on the "chin-side" and flexed on the "occiput-side." This reaction, which Magnus called a tonic neck reflex, usually appeared after a brief latent period and persisted as long as the head was maintained to one

side or the other. Together with his collaborator, De Kleijn, Magnus described many other tonic neck reflexes, such as follow bending of the head backward and forward or bending (not rotating) to one side or the other. They also described a number of tonic labyrinthine reflexes. The latter are outside the scope of this paper, but allusion will be made presently to some of the other neck reflexes. Altogether Magnus has greatly enriched our knowledge of tonus and posture.¹

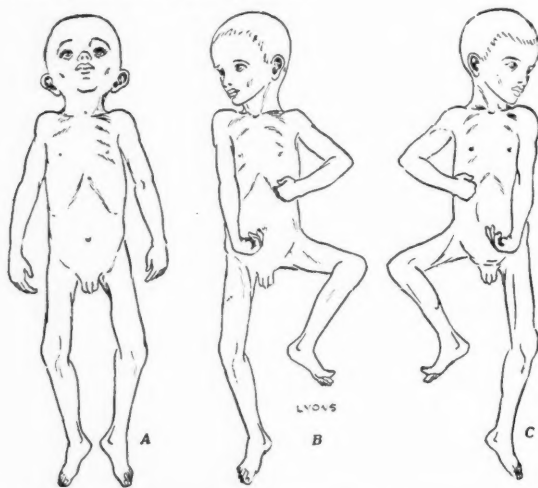


Fig. 132.—Child with tuberculous meningitis: A, Appearance in recumbent position. B, Typical neck reflexes; flexion (with the Babinski toe sign) and abduction on the occiput side; extension and adduction on the chin side. C, Changes in the postures of the limbs on reversing the position of the head. (Wechsler, I. S., *Jour. Amer. Med. Assoc.*, August 15, 1925.)

Very early in the course of their work the Dutch physiologists saw the possibility of the clinical application of the results of their physiologic experiments, and, indeed, recorded some observations² in isolated clinical instances. From time to time a

¹ Magnus, R.: *Korperstellung*, Julius Springer, Berlin, 1924.

² Magnus, R., and de Kleijn, A.: *Weiterdr Beobachtungen ueber Hals und Labyrinth Reflexe auf die Gliedermuskeln des Menschen*, Pflüger's Archiv. f. d. ges. Physiologie, vol. 160, pts. 9 and 10, p. 429, March, 1915.

few European clinicians made similar observations in a variety of neurologic conditions, and in recent years attempt has been made to correlate the physiologic facts with clinicopathologic material. I studied the various tonic and associated reflexes in a number of cases, and the result of the observations with a review of the literature appeared in greater detail elsewhere.¹

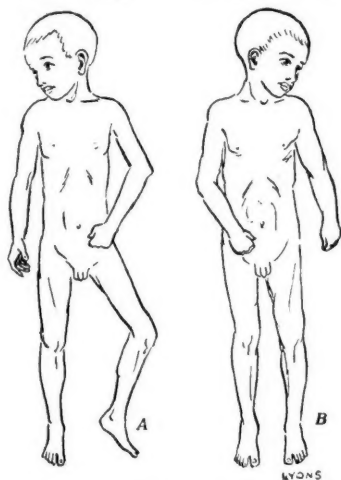


Fig. 133.—Case of tuberculous meningitis: A, Showing less marked postural changes. B, Partial flexion of upper extremity on the occiput side. (Wechsler, I. S., Jour. Amer. Med. Assoc., August 15, 1925.)

Here I would merely speak of the observations which I made in tuberculous meningitis. They have, I believe, some clinical significance.

Before citing cases and discussing the anatomic-pathologic correlations or enlarging upon the possible diagnostic value of the tonic neck reflexes a few prefatory remarks are necessary to avoid misunderstanding. In the first place, one cannot speak of true decerebration in the human being. A complete transverse lesion, such as will induce decerebration in an animal, is incompatible with human life. One, therefore, never or ex-

¹ The Clinical Application of the Tonic Neck Reflexes, etc., Archives of Neurology and Psychiatry, vol. 14, December, 1925.

tremely rarely sees a complete picture of decerebration in man, except possibly before death.¹ The lesions are usually either too diffuse or too minute or too disseminated to give rise to other than fragmentary or incomplete clinical manifestations of decerebrate rigidity. It follows that the tonic neck reflexes elicited in certain cases of brain disease are partial or fragmentary. The flexion or extension, unlike in the animal, may not involve all the limbs equally; and one may observe merely flexion or extension of one limb or partial flexion or extension of a limb, or merely an increase or decrease in tonus (rigidity), depending upon the position of the head. But the point is that the reaction in a given case is always the same, always comes after a latent period, and the posture of the limb is invariably maintained as long as the head is held in the new position. The reflex response obtained in many cases of tuberculous meningitis, whether partial or complete, or whether the result was merely a change in tonus, complied with the physiologic requirements, and hence are true reflexes.

Method of Obtaining the Reflexes.—Observe first the position of the child, whether it lies flat on its back or on the side, and especially the position of the limbs, whether in flexion or extension. It sometimes happens that, as the child lies on one side, the limbs on the side to which the chin is turned are more or less in extension, while those on the opposite side are more or less flexed. This in itself would constitute the position which is the result of the Magnus and de Kleijn neck reflex. Place the child flat on its back and observe the position of the limbs. Then rotate the head to one side so that the chin points to the shoulder (one may have to overcome the neck rigidity). Hold the head in this fixed position. After a few moments note the position of the limbs; observe which flex and which extend. Also feel the limbs to see whether they become more rigid or flaccid. Maintain the head position for a minute or so, then reverse the process by rotating the head to the opposite side. Where the reflex is positive, after a short latent period of a few seconds, one or both

¹ Walshe, F. M. R.: A Case of Complete Decerebrate Rigidity in Man, *The Lancet*, 11, 644, 1923.

limbs on the side to which the chin is turned become extended or show tendency to extension or at least become hypertonic, while those on the other side tend to flex and become less rigid.

Similar reflexes may be obtained by bending (not turning) the head to the side, but the results are not so constant, and the limbs on the side to which the head is bent flex and the opposite extend. On bending the head forward (Brudzinski sign) the limbs flex, and on bending it backward, below the horizontal level, the limbs extend.

Frequently, as pointed out by Walshe,¹ it becomes easier to obtain the Babinski toe sign on the side to which the occiput points. Sometimes, as part of the flexion reflex, a spontaneous dorsal extension of the toe is observed.

CASE REPORTS

Case I.—Infant of nine and a half months. Clinical diagnosis, tuberculous meningitis. Confirmed at necropsy.

Reflexes.—Child lay on left side, chin to the left. Left upper and lower extremities extended, right flexed. Rotating the head, chin to the right, causes extension of the right upper and flexion of the left upper.

Case II.—L. W., three years. Diagnosis of tuberculous meningitis confirmed by demonstration of tubercle bacilli in spinal fluid. Necropsy showed basilar meningitis and internal hydrocephalus.

Reflexes.—All limbs somewhat rigid. Chin to the right; extension of right upper extremity and flexion of left upper. Chin to the left; extension of the left upper and lower extremities, slight flexion of the right upper, with spontaneous right Babinski. Bending head forward causes flexion of all limbs.

Case III.—A. B., sixteen months. Necropsy showed marked pia-arachnoid thickening and yellow exudate at the base of the brain, particularly in the interpeduncular space.

¹ Walshe, F. M. R.: On the Variations in the Form of Reflex Movements, etc., under the Influence of Magnus and de Kleijn's Tonic Reflexes, *Brain*, vol. 46, pt. 3, p. 281, October, 1923.

Reflexes.—Only slight flexion and extension of the limbs on rotation of the head, but marked increase in tonus in the limbs on the "chin-side" and decreased on the "occiput-side," with an occasional spontaneous Babinski on that side.

Case IV.—Eighteen months (?). Clinical diagnosis, tuberculous meningitis.

Reflexes.—Child on its back; all limbs somewhat rigid and extended. Chin to the right; left arm flexed, leg somewhat flexed. Chin to left; left arm extended, right arm somewhat flexed.

Case V.—Baby ten months. Clinical diagnosis, tuberculous meningitis.

Reflexes.—Baby lying on its right side, chin to the right; left upper extremity flexed at elbow, abducted at shoulder, left lower slightly flexed. Head rotated, chin to the left; left upper adducted, markedly extended, left lower extended.

Case VI.—Baby sixteen months. Diagnosis, tuberculous meningitis.

Reflexes.—Occasionally right leg extended when chin was turned to the right; but the tonus increased (*i. e.*, rigidity) on the side to which the chin was turned and decreased on the occiput-side.

Case VII.—Boy three and a half years. Diagnosis, tuberculous meningitis.

Reflexes.—No tonic neck reflexes elicited on rotating the head, but the child lay on the right side, chin to the right, and the right upper and lower extremities were in extension, while the left upper and lower were in flexion.

Case VIII.—Girl two years. Diagnosis, tuberculous meningitis.

Reflexes.—Head rotated, chin to the right; left arm and leg flexed. Chin to the left; right arm and leg flexed.

Case IX.—Boy nine and a half years. Clinical diagnosis, tuberculous meningitis.

Reflexes.—Head rotated, chin to the right; extension of the right arm and flexion of the left. Chin to the left; extension of the left arm and flexion of the right. Doubtful response in the lower extremities.

Case X.—Boy ten months. Diagnosis, tuberculous meningitis.

Reflexes.—Turning the head to the right results in flexion of the left upper and lower extremities, while turning the head to the left results in flexion of the right extremities.

Case XI.—Boy two years. Diagnosis, tuberculous meningitis, confirmed by demonstration of tubercle bacilli in spinal fluid.

Reflexes.—Right upper and lower extremities flex on turning the chin to the left and the left arm extends; on reversing the position of the head, the left arm flexes and the right limbs extend.

NEGATIVE CASES

Case XII.—Child three and a half years. Diagnosis, tuberculous meningitis.

Case XIII.—Child five years. Diagnosis, tuberculous meningitis.

Case XIV.—Child five and a half years. Diagnosis, tuberculous meningitis.

Case XV.—Child five and a half years. Diagnosis, tuberculous meningitis.

Case XVI.—Child eight and a half years. Diagnosis, tuberculous meningitis.

Case XVII.—Child ten years. Diagnosis, tuberculous meningitis.

Case XVIII.—Child eleven years and ten months. Diagnosis, tuberculous meningitis.

Case XIX.—Child five and a half years. Diagnosis, tuberculous meningitis.

Case XX.—Child seven months. Diagnosis, tuberculous meningitis.

Case XXI.—Child two years. Diagnosis, tuberculous meningitis.

Case XXII.—Child eight years. Diagnosis, tuberculous meningitis.

Case XXIII.—Child six years. Diagnosis, tuberculous meningitis.

Case XXIV.—Child seven years. Diagnosis, tuberculous meningitis.

DISCUSSION

The toxic neck reflexes were elicited in 11 cases of tuberculous meningitis and found absent in 13; that is, they were present in 44.5 per cent.¹ In children below three years they were almost constant, while most of the negative responses occurred in older children. The younger the child, then, the more likely the response. Another point worthy of note is that wherever the neck reflexes were found there the Brudzinski sign also was present. The converse was not true.

As far as I know there is only one casual observation recorded in the literature on the occurrence of the Magnus and de Kleijn tonic neck reflexes in tuberculous meningitis.² In the cases observed by me the reflex response frequently occurred only in one limb, or resulted merely in change of tonus. The fragmentary occurrence accords well with the underlying pathology, which will be discussed presently. In some instances they were observed at one time only to disappear later, or only appeared a day or so before death. A number of factors are responsible for their presence at one time and not at another. In any case their presence, I believe, is of grave significance.

I have not observed the tonic neck reflexes in other forms of meningitis, either cerebrospinal or suppurative. Magnus and

¹ Since writing this paper I observed a few more cases of tuberculous meningitis, some of which showed and others did not exhibit the reflexes; the ratio is about the same.

² Simons, A.: *Kopfhaltung und Muskeltonus. Klinische Beobachtungen*, Zeitschrift f. d. ges. Neurol. u. Psychiatrie, vol. 80, p. 499, January, 1923.

de Kleijn¹ report their occurrence in an infant of nine months with suppurative meningitis. From *a priori* reasoning I expected to find them in tuberculous meningitis and not in other forms. This was based on the following theoretic considerations: Tuberculous meningitis generally is a cerebral and not a cerebrospinal meningitis. In a great many instances tuberculous meningitis is basilar, as shown by cranial nerve involvement, and frequently is more marked in the interpenduncular space, that is, the mid-brain region. This, it will be recalled, is the place which if transected causes decerebrate rigidity phenomena. In many cases there is also a tuberculous encephalitis in the brain substance underlying the meninges, transecting, as it were, that part of the brain. Epidemic and suppurative meningitis are more often convexity meningitis, and, what is more important, also involve the spinal meninges and the spinal roots as they pierce the dura. Now, the tonic neck reflexes are abolished experimentally if the upper posterior cervical roots are cut. It is possible, therefore, that the involvement of the roots in the inflammatory process abolishes the reflexes clinically in the other forms of meningitis. The Babinski sign occurs more frequently in tuberculous meningitis. If it is true, as Walshe and Simons hold, that involvement of the pyramidal tract is essential to the occurrence of decerebrate rigidity phenomena, we have additional reason for the presence of the reflexes in tuberculous meningitis.

I would not be understood to say that my explanation is necessarily either complete or applicable to all cases. To one who has worked with the reflexes or, indeed, with the application of any physiologic data to clinical medicine, there are so many disconcerting facts that one can merely venture an opinion and very diffidently at that. For instance, opisthotonos² with marked neck rigidity and retraction of the head, which are assumed to be decerebrate rigidity phenomena, occur more often in cerebrospinal meningitis. The Brudzinski sign also occurs in all forms of meningitis. Now, it has seemed to me that this sign is a defi-

¹ Ibid.

² Bazett and Penfield look upon this more as a sign of irritation due to secondary hemorrhage or infection and not primary decerebration.

nite tonic neck reflex because in experimental animals the limbs flex on bending the head forward and extend on bending it backward. Magnus and de Kleijn also interpret the sign as a tonic neck reflex and so do Boehme and Weiland.³ Brudzinski himself did not know their physiologic significance, although he gave an explanation which, in the light of our present knowledge, may be correctly interpreted. He² thought that the flexion of the legs was due to influence of the extension of the back and neck muscles on the flexors of the leg. Freudenberg¹ elicited the Brudzinski sign in infants in the first three years of life, and (with another maneuver) in babies with rickets.

That the tonic neck reflexes in tuberculous meningitis are elicited more often in infants and very young children is of some significance. My explanation is as follows: All children are born more or less "decerebrate." That is, the cerebrum, and especially the cortex, does not as yet function, whereas the lower centers do. The pyramidal tracts and other cortifugal paths are not myelinated at birth. As the child develops it becomes more and more "cerebrate." Early in life, therefore, it is comparatively easy for a small lesion to cause "decerebration," while later on, as the pathways become fixed, the process of "decerebration" becomes increasingly more difficult unless the lesion be very large. This is borne out by other observations. Thus Minkowski⁴ observed tonic neck reflexes in human fetuses of two to five months which he obtained after cesarean section under novocain. The neck reflexes have never been observed in normal infants.

There are a number of other physiologic and clinical observa-

¹ Boehme and Weiland: *Zeitsch. f. d. ges. Neurol. u. Psychiat.*, vol. 44, p. 94, 1918.

² Brudzinski, J.: Un signe nouveau sur les membres inferieurs dans les meningites chez les enfants, *Archives de Med. des enfants*, vol. 12, No. 10, p. 745, October, 1909.

³ Freudenberg, E.: Der Morosche Umklammungsreflex und das Brudzinskische Nackenzeichen als Reflexe des Sauglingsalter, *Munch. med. Wochen.*, p. 1646, 1921.

⁴ Minkowski, A.: Sur les mouvements, les reflexes et les reactions musculaires du foetus humaine de 2 a 5 mois et leurs relation avec le systeme nerveux foetal, *Rev. Neurol.*, vol. 37, p. 1105, 1922.

tions with references to the neck reflexes which require detailed discussion; but as this has been taken up in another paper¹ I shall make brief mention of their occurrence in other clinical conditions in children. Magnus and de Kleijn observed them in newborn infants with intraventricular hemorrhage; also in 2 patients with hydrocephalus, one a child of three years and another of six; and again in a sixteen-month-old infant with amaurotic family idiocy. De Bruin² observed them in a girl of fifteen months with amaurotic idiocy. Dollinger³ found the reflexes in 1 of 3 cases of Tay-Sachs' disease. Brouwer⁴ described them in a thirteen-month-old baby with meningo-encephalitis. I have also observed them in 1 case of meningo-encephalitis.

Finally, it is of interest to mention "a symptom first described by Binda and believed by him to be almost pathognomonic of tuberculous meningitis. The sign consists in a sudden raising and forward projection of the shoulder, following rapid passive rotation of the head to the opposite side." Neither Tronconi,⁵ who elicited the sign in 7 cases of tuberculous meningitis, nor Binda, who first described it, correlated it with the Magnus tonic neck reflexes; but I believe it could be given such an interpretation. In any case it would seem to lend weight to my own observations.

CONCLUSIONS

The clinical sign elicited is the result of the application of the physiologic tonic neck reflexes of Magnus and de Kleijn to tuberculous meningitis. Their occurrence only in about 50 per cent. of cases weakens their diagnostic significance to some extent, but the fact that I have not observed them in other forms of meningitis gives the sign some clinical value. That the reflexes have been observed in isolated cases of amaurotic family

¹ Ibid.

² de Bruin, J.: *Idiotia amaurotica progressiva familiaris infantilis*, Absts. in *Jahrbuch. f. Kinderheilkunde*, vol. 81, p. 460, 1915.

³ Dollinger, A.: *Zur Klinik der infantilen form der familiären amaurotischen Idiotie*, *Zeitschr. f. Kinderheilkunde*, vol. 22, p. 167, 1919.

⁴ Brouwer, B.: *Ueber Meningo-encephalitis und die Magnus-de Kleijn-schen Reflex*, *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, vol. 36, p. 161, 1917.

⁵ Tronconi: *Shoulder Phenomenon in Tuberculous Meningitis*, Abstr. from *La Pediatria*, September, 1921, *Jour. Nerv. and Ment. Diseases*.

idiocy, which never comes up for differential diagnosis, and in 2 cases of meningo-encephalitis, which occasionally does, is of importance. The significance of the reflex in tuberculous meningitis is that it seems to occur with considerable frequency, especially in infants and children under three years, and, when present, with entire consistency.

That the reflex may occur in any case where the pathologic process happens to involve the midbrain is altogether in accord with physiologic fact. Its occurrence in tuberculous meningitis is merely clinical proof of what is known of its pathology, namely, that it is frequently or preponderatingly a basilar meningitis. For the present the tonic neck reflexes have great physiologic importance. Only further observation will reveal whether they also have clinical significance. But whenever possible it is of importance to correlate the clinical observation of the neck reflexes with the anatomic-pathologic findings in order that light may be thrown on the underlying physiologic concepts of brain function.

CLINIC OF DR. BLAKE F. DONALDSON

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A TREATMENT OF ARTHRITIS

At the beginning of any discussion on the treatment of arthritis it is well to bear in mind that the cause of arthritis is unknown. We may strongly suspect that the proliferative type is of infectious origin, and that several or many factors combine to give us the picture of the degenerative type, but we do not know. And until we do know treatment will remain to some extent unsatisfactory. To add further to our difficulties a differential diagnosis between the two types at times cannot be made, and both types may often be benefited by similar treatment. During the war there was an opportunity to study a group of 6 cases with compound comminuted fractures of the extremities, treated at No. 1 Hospital in Paris. These gunshot wounds had all been badly infected. After an effort to reposit the ends of the bones, and the institution of drainage, the wounds had been closed for a period of six months. For the same period of time there had been no fever, local swelling, or redness. Non-union of the fracture in these cases was due to malposition of the fragments or interposing fascia or muscle.

At operation for non-union a Gram-stain of a smear from the bone-marrow in the end of the bones showed the presence of a Gram-positive diplococcus. Cultures made from the ends of the bones showed *Streptococcus hemolyticus* in pure culture.

The temperatures of the patients were usually immediately markedly elevated, and streptococcus pus was pouring out of the wound in twenty-four hours.

It was truly a remarkable demonstration of the ability of a relatively high-grade organism to live for months without marked local reaction in the body. And it was for this reason that it was

considered inadvisable to operate on compound fractures for non-union until the wounds had been healed for at least nine months.

The oft-noted relationship of sore throats, abscessed teeth, growing pains, chorea, scarlet fever, peritonsillar abscess, carditis, and arthritis casts suspicion on the streptococcus as either a primary or secondary invader of the joints. If this is the case, it seems idle to imagine that removal of the original focus will modify the joint condition in any way other than to prevent additional infection. And clinical observation seems to bear this out. In the very few cases of arthritis who experience after tonsillectomy immediate relief of pain or swelling or stiffness, it is probable that we are dealing with a joint irritated by an exogenous toxin. These cases seldom show radiographic evidence of a joint lesion.

If we are dealing, in some of our cases, with a long-lived non-suppurating type of joint infection, we need what Ehrlich called "sterilisatio magna." But chemotherapy offers nothing new that is of proved value. O-iodoxybenzoic acid is on trial.

Our success with salvarsan and neosalvarsan administration has probably made us somewhat contemptuous of the dangers of intravenous medication. These are very real. The autopsy reports of St. George,¹ the assistant director of laboratories at Bellevue Hospital, on 5 deaths after mercurochrome administration, should be kept in mind. In most intravenous medication the probable mode of action, even with the autogenous vaccines, is only that of a non-specific irritant in the bloodstream.

Of the many drugs which have been tried it seems that salicylic acid has been the most useful of all; and yet, in recent years, its use has been discredited until, by many observers, it seems to be regarded as nothing more than an indifferent analgesic. Cecil and Archer² in a recent paper do not even mention it.

In practice it seems to be our most effective therapeutic agent.

¹ Jour. Amer. Med. Assoc., 85, 2005, 2008, December 26, 1925.

² Ibid., 87, 641, September 4, 1926.

It was in the hope that some more efficient method of administration might be found that in 1923 we began to use sodium salicylate and acetylsalicylic acid in intensive doses over long periods of time. Eighteen months was arbitrarily chosen as the minimal length of time during which large doses should be steadily administered. After a number of changes the following general plan of administration has been evolved: The patients at the beginning of treatment are kept saturated with the drug for from three to seven days. This is done by the administration in retention enemas, twice a day, of from 50 to 100 grains of sodium salicylate, in 2 ounces of a vehicle of thin boiled starch solution. A stock bottle full of this vehicle may be made by putting 2 drams of either laundry or cornstarch in 12 ounces of water, boiling hard for five minutes, and allowing it to cool. The retention enema should be given through a 4-ounce funnel inserted in a large bladder catheter. A clip on the catheter makes the injection easier to manage. Patients can be trained to give these injections unassisted if necessary.

Some action on the auditory nerve is usually noted after the second injection. The patients complain of deafness or ringing in the ears. Rarely does a dosage of 100 grains twice a day cause vomiting.

Following the course of retention enemas, sodium salicylate or acetylsalicylic acid is given by mouth, usually in doses of 10 to 15 grains, with food, three to four times a day. Care is taken that the drug is swallowed in the middle of the meal. Because of the danger of upsetting the chemical balance in the blood no soda is given with it.

This routine is followed daily for three months, and then on alternative weeks for the next fifteen months, so that at the end of eighteen months the patient has received approximately 16,000 grains of sodium salicylate or acetylsalicylic acid. The body tolerates some salicylic acid derivatives amazingly well. We have been perhaps fortunate in not encountering renal or gastric irritation. Each case has been watched as to kidney function, especially for the finding of red blood-cells in the urine. So far we have not noted it.

Of 50 cases started on treatment, only 10 have faithfully carried out the plan. And of this group, 6 were private patients and 4 were seen at the clinic. Most of the remaining cases stopped treatment because of symptomatic relief which seemed to them adequate. Two cases stopped because they considered the treatment not helpful. A number of cases for prophylactic treatment after chorea and initial attacks of acute rheumatic fever stopped treatment at the fourth month. One case has gotten quite out of hand. Suffering acutely with a proliferative type of arthritis which had progressed to the stage of partial bony ankylosis, involving both wrist-joints, she was started on treatment. Finding herself able to resume her work when she took 70 grains of acetylsalicylic acid a day, and suffering pain and increased periarticular swellings whenever she reduced the dose, she has refused to stop it. And, as her history has been checked by her family's statement, it is fair to believe that she has taken over 76,000 grains of acetylsalicylic acid in the last three years. She does not complain of gastralgia. Kidney function is good. She is still much under weight—her original condition. This case should also be classed with the failures of treatment.

As a rule in the line of physiotherapy only active exercise was used. Each patient was required to bend each affected joint rapidly and with considerable force twenty times three times a day. Where possible, and it usually was possible, a walk every morning of two miles in thirty-six minutes was required. A good posture and deep breathing was requested while walking. In order to maintain maximal strength and resistance to infection an effort was made to keep all patients at a normal weight. Too often in fattening or reducing diets the patient's mental incapacity to stick to a diet, which requires the constant exercise of good judgment for its selection, is forgotten, so that certain big classes of food should be allowed or absolutely forbidden. For instance, if any breadstuff of any kind is allowed obese patients, they rarely are successful in losing weight. And in cases of malnutrition our main success in treatment seemed to come when we eliminated all vegetables and salads except potatoes.

Both malnutrition and obesity seem to demand a normal daily amount of exercise to secure results in treatment. Where a patient was overweight an effort was made to reduce at the rate of 7 pounds a month. The diet used was as follows:

HIGH CELLULOSE AND ANIMAL PROTEID, LOW CARBOHYDRATE, AND FAT DIET

Breakfast:

Raw fruit.

All bran cooked and crumbled—3 tablespoonfuls with skimmed milk to cover. Part of the portion of raw fruit may be cut up on it.

One egg—soft boiled or poached.

Coffee or tea with hot milk.

Midday and evening meal:

Lean meat, or fish, or chicken (a good sized portion without thickened gravy or cream sauce).

Two vegetables other than potatoes. They must be prepared without cream sauce.

Salad without olive oil.

Raw fruit.

Nothing made from flour, sugar, or potato is permitted.

A daily walk of two miles in thirty-six minutes on level ground is requested.

This should be done either before or ninety minutes after breakfast.

For patients who were underweight the following diet was used:

HIGH CARBOHYDRATE, FAT, AND PROTEID DIET

Breakfast:

Raw fruit on which 3 teaspoonfuls of granulated sugar is put.

Cereal—oatmeal, cornmeal, or boiled rice, with cream and 3 teaspoonfuls of granulated sugar.

One egg—soft boiled or poached.

Three pieces of bread or toast with butter.

Coffee with cream and 3 teaspoonfuls of sugar.

Midday and evening meal:

Fat meat (chops, steak, roast breast of lamb, roast beef, or roast ham—hot or cold—lamb or beef stew).

Potatoes.

Bread and butter, or rolls and butter.

Rice pudding, or ice-cream, or cornstarch or tapioca pudding or rich cake.

Three pieces of candy at end of noon and evening meal.

Coffee or tea with cream and 3 teaspoonfuls of sugar.

Walk two miles in thirty-six minutes every morning.

No water with meals, milk, soup, chicken or fish, vegetables other than potatoes, salad or fruit dessert is permitted. Drink 6 glasses of water between meals.

Patients were warned against putting too much faith in measures which simply temporarily relieve pain by increasing

blood-flow through affected joints. Although not evidently curative, it would seem that heat, in any form that is agreeable, should be used as a measure to increase the patient's comfort. Far more attention was placed on active exercise than on massage or passive motion. Cathartics and colon irrigations and vaccines were not used. In the frankly degenerative types of arthritis no set plan in the administration of salicylates was followed. They were used to control pain.

No cases of syphilitic, tubercular, or gonorrheal arthritis are included in this group, although it is our opinion that cases of gonorrheal arthritis do better with intensive salicylate treatment than with gonococcus vaccine.

REPORT OF CASES

Case I.—H. J. S., a physician, thirty-nine years of age, was seen at his home on February 1, 1924. He was confined to his bed, having run a continuous fever averaging 104° F. for two months, with a very severe attack of polyarthritis of the proliferative and periarticular type. He was suffering great pain, especially in his markedly swollen knee-joints.

He had had lumbago when an intern at Bellevue in 1910. For the next three years he suffered with a severe neuritis of the right sciatic nerve. He had four attacks of tonsillitis in 1918. Bone pains were severe in 1921. Four days after a tonsillectomy in 1922 the patient developed a very severe polyarthritis, from which he did not recover for several weeks. The present attack, starting December 23, 1923, had been managed as follows:

Small doses of sodium salicylate—salophen—and salicon had failed. Forced fluids and baking treatments had not helped. Injections of boiled milk had exaggerated all symptoms. An autogenous vaccine was being contemplated as the next step when the patient was first seen. He was persuaded to try the routine that has been previously described. With his first injection of 120 grains of sodium salicylate all symptoms were abated. The temperature became normal in two weeks. He took in all 17,000 grains of salicylate up to September 1, 1925.

He has had no recurrence since then. He is carrying on a very

active practice. Seen September 30, 1926 he showed no signs of arthritis or carditis. He had no evidence of renal irritation.

Case II.—L. T., a schoolgirl, aged thirteen, was first seen on June 24, 1925. She gave a history of polyarthritis in 1917, when she had to be wheeled around in a chair because of swollen tender ankles. She had had occasional attacks of tonsillitis. She had been told that she had a "leaking heart" after an attack of pneumonia when two years of age. Physical examination showed evidence of a proliferative type of arthritis involving the cervical spine and shoulders, and a marked carditis. The child was much undernourished and pale, the overacting, markedly enlarged heart seemed to shake the whole chest. The valve lesions were a mitral stenosis and insufficiency. Rest, digitalis, bromids, and salicylates all seemed to help. In September, 1925 a pair of markedly diseased tonsils were removed under ether anesthesia. Salicylates were then given as described before. She has received to date about 10,700 grains of sodium salicylate. She has made amazing improvement, having already gained 50 pounds in weight. The apex of the heart is only 10 cm. to the left of the midsternal line. Overaction of the heart is much less noticeable. She has no stiffness of any joints. She is able to play tennis and attend school without restriction. She shows no sign of any renal irritation.

Case III.—O. H., aged twenty-three, is our most interesting case for the clinic, and our most notable failure under treatment.

He was first taken sick in September, 1913, with pain in the right hip; this pain spread to other large joints. By other doctors he was accorded several different kinds of treatment, including vaccines and a tonsillectomy. He had a fistula in ano operation in January, 1923, when he showed signs of a generalized proliferative periarticular arthritis involving mainly the hips and lumbar spine. He walked with some difficulty. He did not improve under salicylates and was sent to Palm Springs, California. After a few weeks there he suddenly discharged some pus by rectum and began to have very great pain in both hips, with a

fever of 104° F. The fever abated somewhat and he was brought back East in a cast. Radiographic examination showed a destructive process in both hip-joints. Fibrous ankylosis had already developed. Successively the knees, ankles, spine, and shoulders and wrists were involved. Three attempts under anesthetics were made by an orthopedic surgeon to maintain active motion in the hip-joints. With the last attempt the left hip was fractured. The ends of the bone being in good position, he was then left alone.

By the most rigid active and passive exercise about 10 degrees of motion has been maintained in both knees. He was seen in consultation by Dr. Ralph Pemberton in 1925, when confined to bed. Since then he has been able in steadily increasing periods to get out of bed, with assistance. He can now, by using a cane, take about seventy steps before getting much fatigued. He has developed his shoulders to the extent of being able to hit a punching bag thirteen hundred times without missing. All this while (since September, 1923) he has been on salicylates. Most of the time up till August, 1926 he has taken 70 grains of acetylsalicylic acid a day. It was the only method that could be found to relieve his intense pain. The pain is now much relieved and the medicine is reduced to 30 grains a day. When we are sure all danger of recurrence is past an arthroplasty on the right hip is contemplated.

We may summarize then, this treatment which we have found useful so far, as follows:

1. The administration by retention enemas, and by mouth, of from 10,000 to 20,000 grains of sodium salicylate or acetylsalicylic acid over a minimal period of eighteen months, in an effort to prevent recurrence.
2. The maintenance of normal weight.
3. The intensive use of active exercise for every affected joint.

We are showing these few cases too early to even call this a preliminary report. Rather it is the outline of a plan of treatment. It is our opinion that ten years' observation is needed before reporting on the treatment of a group of arthritis cases.

CLINIC OF DR. JOSEPH S. DIAMOND

BETH ISRAEL HOSPITAL

SOME CONSIDERATIONS OF THE PATHOLOGY AND DIAGNOSIS IN DISEASES OF THE LIVER AND BILI- ARY TRACT

THE recent advances in the physiology of the liver and the development of various tests for its functional capacity have added a brilliant chapter to modern medicine. They have given us a better insight into the complexity of some of its functions and have helped to recognize and differentiate, in some instances, the type of pathological process which is going on.

From Rous and McMaster¹ we have learned of the large factor of safety that the liver possesses, and that but 15 to 20 per cent. of liver tissue is required to carry on the normal metabolic processes. Removal in animals of four-fifths of the liver tissues or ligation of the major parts of the circulatory and biliary radicals does not interfere with the normal metabolic function, neither does jaundice develop.

From Mann, Bollman, and Magath^{2, 3, 4} we have learned that the liver is the sole regulator of the blood-sugar level. When the liver is extirpated the sugar level drops and the animal goes into a condition analogous to the hypoglycemia of insulin shock. We have known that it forms and stores glycogen, but this glycogenic function is dependent upon the pancreatic hormone. In the absence of the pancreas this glycogenic function is entirely lost, and is only re-stored by administration of insulin. It stores and saturates fats. When liver glycogen is diminished the fat storage is increased. It is the main organ concerned with the production of urea and destruction of uric acid.

As to bile-pigment formation Mann and his co-workers have shown that bilirubin, which has been heretofore regarded

as a sole product of the liver cells, can be formed by other organs in the body outside of the liver. Within a few hours after the total removal of the liver in the dog bile appears in the urine, the sclera assume an icteric tint, the blood-serum shows a marked increase in bilirubin, and postmortem the fat and all the tissues and body fluids are bile stained. This evidence indicates that the reticulo-endothelial apparatus, of which the Kupfer cells of the liver are a part, deal with the formation of the bile-pigment. Under normal conditions the Kupfer cells are mainly concerned with this function; while in the absence of the liver other endothelial cells lining the capillaries take up this function.

In addition to the manifold functions enumerated, the liver is the only organ that forms bile salts. It produces and eliminates cholesterol. It retains the iron as it is broken up from the hemoglobin molecule. It deals with the formation of fibrinogen and regulates blood coagulation. It has a powerful detoxicating function, neutralizing substances which are brought to it from the intestinal canal as well as from the general circulation.

The liver must, therefore, be regarded as a complex laboratory, capable of metabolic, excretory, and detoxicating functions, being endowed at the same time with a large power of reserve. In diseased states any one of these functions may be interfered with, differing in this respect from other organs. Only in severe states, such as phosphorus, arsenic, or chloroform poisoning, or in acute yellow atrophy, may these functions simultaneously be involved.

In taking up the question of liver function it becomes therefore apparent that it is futile to speak of functional tests for the elaboration of the capacity of the liver as a whole, for each test can only deal with a specific phase of liver function, such as testing out the carbohydrate function, or its behavior to bile-pigment, or the excretory capacity of foreign substances, etc. What is more important, however, is the aim to utilize these tests in the differential diagnosis as to the type of pathological lesion which is going on. The tests employed today may be divided into several groups:

1. Bile-pigment retention.

2. Excretory function.

3. Metabolic.

1. The most important bile-pigment retention tests are the Van den Bergh⁵ and the icterus index⁶ tests. Both deal with the estimation of the amount of bile-pigment in serum. The Van den Bergh test consists in the formation of azobilirubin and is a direct reaction which takes place with the bilirubin and Ehrlich's diazo reagent and gives rise to a purplish-red color. The icterus index test is one dependent upon the comparison of the color of the serum with a standard of bichromate solution 1 : 10,000. It is needless to say that the icterus index test is subject to errors, as many other substances, such as occur in diabetes, etc., will produce a yellowish discoloration of the serum. Under ordinary conditions, however, the test can be employed with a fair degree of accuracy.

The chief value of the estimation of bilirubin in the serum is to determine the so-called latent icterus or subicteric state. There occurs in this condition an increase of bile-pigment in the serum before visible evidence of jaundice becomes apparent, when the sclera may be but faintly discolored, long before bile appears in the urine. This is an important diagnostic aid. Such increase of pigment in the serum is found in acute cholecystitis and shortly following attacks of gall-stone colic. No increase in bile-pigment is found in chronic cholelithiasis.

In active states of jaundice the quantitative estimation of bile-pigment in the serum can be used to advantage in ascertaining the progress of the disease, where repeated examinations will give us information as to the degree of jaundice, and also whether the disease is progressing or abating. This is important in detecting a complete mechanical block of the common duct. Aside from this, this test is employed in hemolytic diseases and the so-called states of dissociated icterus where the pigment alone is retained in the serum, but not the bile-salts.

2. The excretory tests depend on the ability of the liver to eliminate foreign substances. These comprise dyes, such as phenoltetrachlorphthalein, indigocarmin, methylene-blue, mercurchrome, etc. Of these, the Rowntree phenoltetrachlorphtha-

lein test, as developed by the Rosenthal⁷ method, is the best. This consists of an intravenous injection of the dye, in the proportion of 5 mg. per kilogram of body weight, and the blood-serum re-examined at the end of one hour for the presence of the dye. Normally, the dye is rapidly removed from the bloodstream, so that at the end of one hour mere traces of the dye or none at all remains. The liver, having an affinity for this dye, takes it out of the general circulation and eliminates it through the bile-stream. The retention of the dye parallels roughly the degree of retention of the bile in the serum in jaundiced conditions. In obstructive jaundice, with block of the common duct from stone or other external causes, the retention of the dye reaches very high figures. Such retention does not indicate hepatic insufficiency, but merely a mechanical interference to the channels eliminating this substance. That the intravenous introduction of this dye is not entirely innocuous has already been sufficiently mentioned before in the literature. Thrombosis of the veins of the arm developed in a goodly percentage in the cases of our series⁸ at Bellevue Hospital; also chills and a rise of temperature, and in 1 case, the patient who was recovering from catharral jaundice, developed a sudden sharp pain in the hepatic region, with a return of the jaundice lasting several weeks. Since the writing of this paper tetrabromphenolphthalein (bromsulphalein) has been introduced, which is less irritant and less toxic and enjoys greater concentration, so that but 2 mg. per kilogram of body weight are required.

3. Metabolic: (a) The urobilogen test in the urine, (b) the carbohydrate tolerance tests where levulose and galactose are employed. The galactose test has received favorable reports abroad. It consists of the administration of 40 gm. of galactose on a fasting stomach and the urine collected for four to six hours and estimated for the amount of galactose eliminated. Under normal conditions from $\frac{1}{2}$ to 2 gm. of galactose may be found. The elimination of more than 2 gm. has been regarded as significant of liver insufficiency. In our series of cases conducted for the comparative study of various liver function tests we have not found the galactose test to be of much value. In

many conditions where the other tests gave positive findings, the galactose in the urine did not exceed 2 gm., with the exception of 2 cases. While experimentally, in severe phosphorus or chloroform poisoning, the animal may show a diminished tolerance for galactose, this is, however, not found in subacute or chronic liver affections.

Urobilogen Test.—In the urobilogen test in the urine we possess a very simple test which can be carried out by any one with more simplicity than the ordinary albumin or sugar reactions. It consists of the addition of 1 c.c. of Ehrlich's aldehyde reagent (2 gm. paradimethylamidobenzaldehyde, dissolved in 100 c.c. of a 20 per cent. hydrochloric acid solution) to a test-tube of urine, upon which a red color develops. The intensity of the red color varies with the amount of urobilogen in the urine.

Since 1922 Dr. Wallace and the writer⁸ have conducted a series of experiments in animals as well as a large number of clinical observations in man, for the purpose of studying the significance of urobilogen in the urine. The physiological conclusion as to the mode of origin of urobilogen have been substantiated in toto by similar independent investigations of MacMaster and Elman.⁹ Aside from hemolytic diseases where blood destruction is taking place, the presence of the urobilogen in the urine indicates liver disease. We have introduced a simple quantitative method of its estimation which consists in a series of dilutions of the urine in water until the pink color is no longer discernible when the Ehrlich's reagent is added to it. The value of the urobilogen test is manifold, for it tells us not merely of the hepatic insufficiency, but it helps us also to differentiate the type of jaundice, or the particular disease which brings about the jaundice. Jaundice can be divided into three main groups:

1. The obstructive type, which is the result of an interference with the flow of bile in the larger ducts. These are due to mechanical causes, such as stone within the common duct, or occlusion of the duct from inflammatory changes, or atresia from cicatrization following operations. Or it may result from press-

ure from without, such as carcinoma of the head of the pancreas, or from malignancy from any of the neighboring organs, or from pressure of enlarged glands, such as Hodgkin's, etc.

2. Hepatogenic, due to parenchymatous disease of the liver cells, such as takes place in toxic states, catarrhal jaundice, liver poisonings, acute yellow atrophy, etc.

3. Hemolytic, where hemolysis or blood destruction is taking place, such as primary anemia, familial or acquired jaundice, malaria, and other parasites causing hemolysis.

Origin of Urobilogen.—Urobilogen is formed from the bile-pigment bilirubin as it reaches the large bowel, there, by a process of decomposition brought about by the action of the putrefactive micro-organism, the bilirubin is changed to urobilogen. The urobilogen passes out with the feces. Some of it, however, is absorbed through the portal circulation and is carried to the liver, there to be utilized, probably synthesized, to higher products. Some of it, however, escapes into the general circulation and from there eliminated in the urine. The kidney has a low threshold for urobilogen and eliminates it promptly. Traces are found normally in the urine. In examining a large series of normal patients, including medical students, we found with our method of estimation, that the urobilogen may be present up to dilutions 1 : 20. In diseased states it may go up to several hundred dilution and in a few instances we found it as high as 1:1000 to 1:1500 dilution. When the liver is diseased the urobilogen, which is carried through the portal circulation into the liver, cannot be properly utilized and is shunted into the general circulation.

The fact that the urobilogen is formed in the intestinal canal from the bile-pigment is made use of to great advantage in differentiating a mechanical obstructive jaundice from a hepatogenic one. In obstructive jaundice with a complete block, such as occurs in carcinoma of the head of the pancreas, urobilogen is never found in the urine because no bile enters the intestinal canal. On the other hand, in jaundice due to parenchymatous liver diseases, such as catarrhal jaundice or other toxic forms, bile is never completely absent from the intestine and

urobilogen appears in the urine in very large quantities. Blockage due to stone is seldom complete, and therefore in this condition urobilogen is seldom absent from the urine. Even though it may not be increased if there be an accompanying cholangitis, however, the urobilogen output rises to very high figures. The importance of this fact cannot be too strongly emphasized. Difficulties are encountered daily in the differential diagnosis as to the type of jaundice which presents itself before us. In the obstructive types surgery is indicated in many instances without delay, while in the toxic types surgery is never indicated no matter how severe the condition may be. The phenoltetrachlorphthalein test, the Van den Bergh, and the icterus index test do not help much in this differentiation, as these merely indicate a high retention. The repeated examination of the bile-pigment in the serum may give us a clue as to the progression of the disease.

In chronic diseases of the liver, such as cirrhosis, or in heparlobatum of syphilis, the dye retention may often be the only test that will be outstanding of all the others. The argument that one may advance here is that the liver has gradually accommodated itself to the performance of its daily metabolic functions, but when foreign substances are suddenly introduced they cannot be acted upon.

THE EXTRAHEPATIC BILIARY TRACT

Diseases of the extrahepatic biliary tract comprise the most common abdominal pathology. They occur more frequently than peptic ulcer and appendices combined. Their symptoms masquerade under all forms of reflex gastric disturbances and may vary from a slight digestive distress to a life-long invalidism, or death may supervene in a short time upon the picture of an acute surgical abdomen or a fulminant septic state. The disease may be confined to the gall-bladder or reach the larger ducts, and occasionally spread to the minutest ramifications of the biliary radicals in the liver, involving at times the liver cells as well.

In protracted states these chronic inflammatory processes may lead to cirrhotic liver changes. Occasionally the large

biliary passages, including the gall-bladder, may undergo malignant degeneration.

The pathogenesis of the biliary tract still belongs to the domain of speculative medicine. The formation of gall-stones is still a mooted question and chapters are still being written on the physiology and anatomy of the gall-bladder.

PHYSIOLOGY OF THE GALL-BLADDER

In the light of recent investigations it becomes more and more apparent that the gall-bladder must be regarded as a vestigial organ, rendering but little service to the human economy. Many species of animals, like the elephant, horse, rat, etc., are devoid of gall-bladders. No untoward effects have ever been observed from the innumerable cholecystectomies in man. Its power of concentration is offset by its small size which is insufficient to regulate the large amount of bile eliminated by the liver during the twenty-four hours. Its function must be considered merely as one of a slight overflow receptacle in the nature of a diverticulum of the common duct, devoid of contractile powers, which is merely able to receive small quantities of bile whenever the intraductal pressure rises higher than usual, the emptying of the gall-bladder being merely a passive act dependent upon mechanical factors, such as pressure from an engorged liver during the digestive period.

Some experiments carried out by Crohn¹⁰ and later by the writer,¹¹ which consisted of injecting carmin into the gall-bladder, revealed that the gall-bladder did not discharge its contents in ten days, some of it still remaining after a month's time.

The writer's experiments were supplemented by the establishment of a duodenal fistula, through which a cannula was introduced, so that injection of magnesium sulphate, hydrochloric acid, peptones, etc., could be introduced daily with the animal in the waking state. These were done in order to carry out the idea of the Meltzer-Lyon contrary-innervation action. In these experiments the gall-bladder did not discharge its contents. Occasionally microscopic carmin granules could be seen.

Upon the autopsy the gall-bladder was still found full with the carmin at the end of ten days to two weeks. Only the portion nearer the neck contained some bile, there being no admixture with the carmin in the fundus. That the cystic duct remained patent was seen by the fact that when the fundus was lifted up the carmin readily poured out.

In approaching the subject of gall-bladder pathology from the clinical standpoint, and considering the symptoms of abdominal colic, reflex gastric disturbances and radiations of the pains, we ask ourselves what are the factors which give rise to this triad of symptoms. There are three main considerations:

1. The neuromuscular apparatus of the cystic duct, the relative position and anatomic structure of the gall-bladder.
2. A disordered cholesterin metabolism, leading to stone formation.
3. Infectious processes with and without gall-stone formation.

Anatomical Considerations.—Recent anatomical studies of the gall-bladder, especially by the Swedish surgeon Berg, Schmieden, Luetkens, and also studies of its neuro-anatomy by Westphal, have introduced a new factor in the elucidation of the symptom-complex of the gall-bladder colic, which may arise in the absence of stones or any evidence of infection. Attention has been drawn to the hump-like character of the neck of the gall-bladder, which upon filling gives the impression of a horse's neck, also to the sphincteric thickening at the beginning of the cystic duct, and to the cork-screw-like shape of the cystic duct. All these cause impediments to the outflow of the bile from the gall-bladder, influencing stasis to a marked degree. The inclusion of the nervous apparatus in the wall of the cystic duct is claimed to control the sphincter of Oddi as well. Disturbances in this regulatory mechanism can give rise to a dyskenetic form of cramps in the gall-bladder region independent of any actual pathology. The spasm of the cystic duct may readily be compared to pyloro- and gastropasm, of a functional character, which can be actuated by similar psychic and emotional phenomena.

Other anatomical and mechanical factors, such as viscerop-

toxis, tight lacing, posture and pregnancy, distort the course and relation of the cystic duct, causing bending and kinking, which still further interfere with drainage.

The static gall-bladder in time gives rise to definite pathological manifestations. While grossly it gives no evidence of pathology, with the exception, perhaps, of some distention, yet microscopically it supplies ample information. Lushka's ducts, which traverse perpendicularly from the mucous membrane into the deeper strata of the gall-bladder and ordinarily are collapsed, now appear distended and deepened, containing débris of epithelia and inspissated bile. There occurs a thinning of the walls of the gall-bladder and a flattening of the mucous membrane. Later there is also a lymphocytic infiltration. It thus forms a *locus minoris resistentia* becoming vulnerable to bacterial invasion either from an ascending or hematogenous origin.

FORMATION OF GALL-STONES

The controversy over the formation of gall-stones still rages unabated, with Aschoff on one side maintaining the metabolic disturbances as the cause, and Naunyn, on the other hand, maintaining the infectious basis only as the cause.

That there is not one single cause responsible for the formation of gall-stones is recognized by all. The *modus operandi*, however, for their formation is still enshrouded in speculative thought. The exact cause for the crystallization of the cholesterol still remains unknown.

We must consider three factors for the formation of stones:

1. Stasis.
2. Disturbed cholesterol metabolism.
3. Infection.

1. The baneful influence of gall-bladder stasis has already been pictured. Aside from predisposition and diathesis, the metabolic factors furnish a very interesting problem.

2. We are indebted to the French school for our knowledge of cholesterol metabolism, especially to Chauffard, Guy la Rooge, and Grigau. The relation between cholesterol and stone formation is often noted. It is known that during pregnancy and

lactation there occurs a marked increase in the cholesterin formation and also in nutritional disturbances, especially in obesity cures with rapid loss of weight there occurs similarly an increased production of cholesterin.

The predilection of cholesterin to the reticulo-endothelial system and its elimination through the Kupfer cells of the liver accounts for the increased cholesterin content of the bile. Recent studies of the relation of bile acids to cholesterin may give us a better understanding of the solubility and sedimentation of the cholesterin substances. Aschoff's¹² observations on the structural characteristics of the stones has led him to the belief that the coarse crystalline radiating cholesterin solitaires which occur in non-infected gall-bladders and are present at all ages in individuals who have never in their life shown signs of disease are the result of disturbed cholesterin metabolism. These stones lack the lamellations which are so characteristic of almost all gall-stones.

The incidence of these stones according to Aschoff form one-third of all varieties of gall-stones, whether alone or in combination forms.

The pure pigmented stone, the bilirubin calcium, is another form which may be regarded as the result of metabolic disturbances. They are, however, rare and seldom occur singly.

3. **Infection.**—The rôle of infection in connection with the formation of gall-stones has been studied by Naunyn.¹³ His belief that all gall-stones are antedated by bacterial invasion into the gall-bladder, giving rise to a so-called "lithogenic" or stone-forming catarrh of its wall, has been substantiated in the main by Kehr.¹⁴ In a series of 100 operative cases, where he sectioned and examined all calculi for their structural characteristics, he found that 83 per cent. were the result of pure infection, 14 per cent. were combination stones plus infectious stone, and only 3 per cent. were radiating stones. Admitting that the radiating stones, according to Aschoff and Bacmeister,¹⁵ are the pure cholesterin stones which are formed from the crystallization of the cholesterin from the bile in a sterile gall-bladder, he found but 17 per cent. which presented such a radiating core, in whom the possi-

bility of non-infection could have been considered. Naunyn is entirely opposed to the non-infection theory. According to him stones are formed from the following three substances: (1) An organic base, (2) calcium bilirubinate, (3) cholesterin. All must contain an organic colloid substance. The inspissated bile contains débris of broken-down epithelial cells from the mucous membrane of the gall-bladder and precipitated stone-forming substance such as pigment and cholesterin. The calcium bilirubinate deposits on a thread of mucus, giving rise to the so-called calcium bilirubin flake. The cholesterin is derived chiefly from the débris of the epithelial cells which lie in clumps or needles. The presence of fibrin or mucin cause the rapid solidification of these masses. All these processes are an expression of inflammatory reaction resulting from an infective process in the gall-bladder or ducts, the so-called "lithogenous cholangie."

In the smaller biliary radicals we find only the calcium bilirubinate stones which are often carried with the bile-stream and dropped into the gall-bladder, there to form the nucleus for a cholesterin stone.

In the more pronounced gall-bladder infections an exudate is poured into the gall-bladder rich in cholesterin and protein. The center of crystallization is supplied by the leukocytes and epithelial débris, and agglutination is favored by the changes in the cholesterol solubility in the tenacious bile.

The **infectious stones** form the largest number of all gall-stones. They include the large group of facetté cholesterin pigmented calcium stones and the cylindrical pigmented calcium stones.

These facetté stones possess a rosetted nucleus which is surrounded by a cortex of numerous lamellæ. The nucleus and cortex consist of the same material, and there is no sharp line of demarcation as in the combination stones of Aschoff and Bacmeister. They possess a framework rich in protein which is entirely lacking in the radiating cholesterin stones and give the clue to their origin, *i. e.*, they are formed in a medium rich in protein.

The **barrel** or **cylindrical-shaped stone** is usually the fixed

stone in the gall-bladder pockets and arises at the point of ulcerations in the mucous membranes of the gall-bladder and possess similar structure as the facettet stones.

The **combination stones of Aschoff and Bacmeister** contain a radiating cholesterin nucleus surrounded by layers of calcium bilirubinate which have been deposited later, indicating a subsequent infectious process.

In the controversy between the metabolic and infectious origin of stones there is still another factor to be considered, of which one hears very little. It is difficult to understand, if infection were the sole cause of stone formation, why do we find so many infected gall-bladders without stones. There must evidently be some other metabolic factor which, when combined with infection, results in the formation of stones. In those where the metabolic factor is absent the infection alone does not lead to stone formation.

THE RÔLE OF INFECTION IN THE BILIARY TRACT

We shall now consider the inflammatory processes of the biliary system which are due to bacterial origin, the manner of invasion of these bacteria, and the types of micro-organisms. The infection may be localized in the gall-bladder, giving rise to cholecystitis, or may spread throughout the entire biliary system, resulting in cholangitis. The predilection and localization of the infectious process in the gall-bladder is due to stasis, whereas there is always a free flow in the ducts. When the free flow is interfered with in the ducts in the presence of an infection cholangitis always results.

Cholangitis.—The study of cholangitis began with Naunyn and Riedel in Germany, and in France with Netter, Gilber, and Dupres. It was first developed in connection with inflammations arising from and associated with cholelithiasis. Later Naunyn¹⁶ developed the study of the pure cholangitis without the presence of stones. He demonstrated in the bile *Bacteria coli* and the typhoid group, and showed that these can lead to a local or general infection, especially when there occurs an interference in the flow of bile. This infectious cholangitis can reach a very

severe degree of virulence, leading often to death without any suppurative process or any recognizable macroscopic changes in the walls of the ducts. In 1891 Naunyn¹⁷ performed the following experiment: He ligated the common duct of a dog and injected into the gall-bladder a watery suspension of a three-day culture of colon bacilli which was obtained postmortem from an empyema of the gall-bladder. Within two days the animal died. The autopsy revealed a distended gall-bladder without any evidence of pus or peritonitis. A pure colon culture, however, was obtained from the bile and from the blood of the heart of the animal. The intrahepatic biliary radicals appeared somewhat distended, the mucous membrane unchanged. On the surface of the liver there were seen punctate whitish foci as well as in the cut section. Similar changes were noted in the kidney and spleen.

A control experiment on a dog, consisting in the injection of a similar culture into the gall-bladder without the ligation of the common duct, gave rise to no symptoms. Eight days later the animal was killed. No change whatever was found.

This fulminant process Naunyn has termed "cholangie," indicating the general involvement of all the biliary radicals from the papilla Vateri to the bile capillaries, differentiating it from cholangitis where macroscopic changes in the wall can be demonstrated and which usually lead to suppurative processes.

The presence of bacteria in the bile has presented several problems of particular interest to the bacteriologist:

1. The mode of entry of the micro-organisms into the bile.
2. The significance of their presence in the bile.
3. The type of flora which is most prevalent and most responsible for the pathologic changes.

1. **The Mode of Entry.**—As to the mode of entry, we must consider the (a) hematogenic, (b) enterogenic, and (c) lymphatic routes.

(a) Earlier views held by Biedel and Krauss were that the liver possesses a physiologic excretory function, and that in the acute infectious disease the liver eliminates the bacteria in the effort to rid the organism of the noxious substances in the same

manner as other eliminative organs, such as the kidneys. More recent investigations, especially by J. Koch and Frankel,¹⁸ through careful histologic studies indicate that the bacteria reach the bile-stream through embolic processes in the capillaries of the entire biliary tract, causing necrosis in the liver, in the bile radicals, and in the gall-bladder, with a resultant discharge of the bacteria into the bile. This conforms to the rule of all generalized infection. In these organs where the speed of the circulation is somewhat lessened there occurs a deposition of bacteria on or between the endothelial cells of the capillaries, and there the conflict between the living cell and the bacteria takes place. The rapid multiplication of the virulent micro-organisms causes the death of the cells by the bacterial toxins, and so there occurs a swarming of large numbers of bacteria into the biliary stream.

(b) *Enterogenic or Ascending Infections*.—In this connection there comes into consideration only one type of micro-organism, *Bacterium coli*, which is the natural habitat of the intestine and is found in abundance in the duodenum at the ampulla Vateri. The typhoid and paratyphoid group, while present in the intestinal canal, do not reach the biliary tract by an ascending infection, but through hematogenous origin. Frankel has injected paratyphoid germs into the peritoneal cavity of animals and was able to recover later pure cultures in the bile.

(c) *Lymphatics*.—Nix, abroad, and Graham Peterman, in this country, believe that the infection may reach the biliary tract through lymphatics which enter the mucous membrane of the gall-bladder and ducts, the infection being carried from foci of the disease elsewhere in the abdomen.

2. The Significance of the Presence of Micro-organisms in the Bile.—The question whether the presence of micro-organisms in the bile always indicates infection of the biliary radicals has been of great interest. Umber¹⁹ raises the issue that simple "bacteriocholie" does not indicate infection of the liver or bile radicals, and that the bile of normal individuals is not always bacteria free. It is claimed, however, that within the normal individual there may be present living micro-organisms which are

in an avirulent or quiescent form which gained entrance through a previous minor skin or mucous membrane lesion. Pathogenic micro-organisms may thus lay dormant for a long period until through any debilitating cause of the body, such as an intercurrent infection, will suddenly become transformed from the erstwhile quiescent state into a virulent form. Many cases of osteomyelitis can be explained in this fashion.

Umber calls attention to a series of observations which he has made during the war, particularly in north Germany, where the frequency of liver infections has been high. He claims that the depletion of the liver cells of their glycogen storehouse, as takes place during long states of undernutrition, increases markedly the susceptibility of the liver to infection, and thus a simple "bacteriocholie" develops into an acute cholangitis.

Davis and Whipple,²⁰ in working out the problem of chloroform anesthesia in dogs, found upon histologic examination that the most profound toxic effects were produced when the animal was starved for a period of three days prior to the anesthesia.

In our own experiments,⁸ we found that we could produce liver damage, as estimated by urobilogen elimination in the urine, amounting from ten to fifteen times higher when the animal underwent a preliminary three-day fast prior to the chloroform anesthesia. We also noted that in such states operation upon the biliary tract was followed by severe cholangitis.

Typhoid Carriers.—The presence of typhoid bacilli in the bile has aroused considerable interest in connection with the so-called typhoid carriers. Cholecystectomy, however, in these individuals has not freed them of the bacteria, indicating the wide-spread infection through the biliary radicals and liver tissue. It is also known that the Kupfer cells have a phagocytic power which can explain the escape of micro-organisms into the bile.

3. Types of Bacterial Flora.—Recent investigations tend to emphasize the importance of various forms of streptococci and their preponderance in the biliary tract infections. Rosenow,²¹ in making cultures of the mulsified walls of diseased gall-bladder, obtained growths of streptococci with which he was able to reproduce cholecystitis in animals by intravenous injections.

There has been some discrepancy between the older and the more recent investigations as to the prevalence of the type of micro-organisms in the biliary tract. The older investigators found a preponderance of the colon group. For instance, Kelly's²² studies of Deaver's 240 cases reveal the following: *Bacteria coli*, 28.33 per cent.; *Bacteria typhosus*, 2.25 per cent.; *Staphylococcus aureus*, 2.92 per cent.; *Streptococcus pyogenes*, .42 per cent.; *Staphylococcus albus*, .85 per cent.; *Bacteria coli* and *Staphylococcus aureus*, .83 per cent. Unidentified, 2.5 per cent.; sterile cultures, 52.92 per cent.

The difference, as can be readily seen, exists in the manner of conducting these examinations. This is best illustrated by Huntemuller,²³ of Giesen, who conducted a series of examinations in 150 cases that came to operation for infection of the gall-bladder and biliary tract. He obtained striking differences between the smears from the bile and from the organs themselves. For instance, he found in the bile examination but .7 per cent. staphylococci, which after forty-eight hours rose to .2 per cent. The colon bacillus was found in 5 per cent. of the cases. If, however, the organs themselves were examined, that is, the material obtained from the walls of the gall-bladder, the cultures yielded positive findings in 100 per cent. of the cases. The liver tissue gave positive cultures in 80 per cent. of the cases. In 60 per cent. of the cases the staphylococcus predominated. The colon bacillus, which was hitherto considered as the chief causative agent in cholangitis, was found but in 12 per cent. The difference is explained by the fact that the colon bacillus extends upward from the intestinal canal, depositing and growing in various strains upon the folds of the mucous membrane of the ducts and gall-bladder, never penetrating the deeper layers of the tissue, while the staphylococci and streptococci, which are hemotogeneous in origin, are found growing in circumscribed nests within the tissue proper.

Brown found streptococci in 30 per cent. of the cases in which there were slight lesions of the gall-bladder, and in 75 per cent. of the cases in which the changes were marked. He concludes that the streptococci are the chief etiologic factors in infections

of the gall-bladder. It is important to bear this in mind in considering the relation between septic foci and infection of the gall-bladder and formation of gall-stones, and also between infected gall-bladders and other infectious diseases, such as acute articular rheumatism, endocarditis, and other cardiovascular and renal diseases.

CHOLECYSTITIS

When infection takes place in the gall-bladder it may be ushered in as an acute process, or it may develop slowly from the start as a chronic process. The acute inflammation may be very slight, a serofibrinous process, or very grave, of a seropurulent character. This takes place usually if a stone becomes blocked in the cystic duct. The process may clear up with the loosening of the stone and the discharge of the purulent material. At times, however, perforation in neighboring hollow viscera may take place and fistula tracts may thus be established.

More frequently the occlusion of the cystic duct causes the formation of a hydrops of the gall-bladder, with either an acute gangrenous inflammation of the walls, or the acute inflammatory condition may subside and the contents become sterile in time. The gall-bladder, however, remains large and its walls thickened and infiltrated with connective tissue.

The infective agents may spread through Lushka's ducts toward the serous coat and cause pericholecystic peritoneal involvement. It may involve the pylorus, stomach, duodenum, colon, pancreas, right kidney, and liver, forming a liver abscess. It may involve the subphrenic space and cause a subphrenic abscess. The right pleura and right lung may also be involved, causing empyema and pulmonary abscess.

I have often found in ambulatory cases with chronic gall-bladder disease the hepatic flexure pulled up and adherent to the right diaphragm in the subdiaphragmatic space, giving evidence of a wide-spread infection which has become localized.

If the infection travels by means of the circulation, we then have thrombo- and pyelophlebitis, endocarditis, meningitis, etc.

The chronic process may either develop as such from the start or may follow the acute state. Chronic ulceration may

continue, leading to intramural abscesses, which may perforate at any time. Or this chronic process may lead to scar tissue formation, causing either hour-glass contraction, or the entire organ may be transferred to the so-called *strawberry gall-bladder*.

The same inflammatory process may take place in the common duct, causing a serous or seropurulent exudate with blockage usually due to both stone and inflammatory changes. Here we have the typical picture of icterus plus the septic form of temperature. The process may clear up if the flow of bile is re-established through the removal of the obstruction at the papilla Vateri or the process may extend into the hepatic ducts, and from there involve all the biliary radicals in the liver, giving rise to cholangitis putrida, with abscess formation through the entire liver substance.

CLINICAL SYMPTOMS OF CHOLELITHIASIS

In the clinical consideration of cholelithiasis we must agree with Kehr that the term "cholelithiasis" does not fully cover the multitude of pathologic entities that manifest themselves with this condition. He argues that the term should be changed to "diseases that lead to and accompany the formation of stones in the biliary tract." For in truth, the stone is merely the product of a condition, a symptom, in other words. We must direct our attention to the existing state prior to the formation of stones, as well as to the condition during their presence and following their removal.

The symptoms must be attributed to the accompanying inflammatory and infective process in the gall-bladder and ducts. In other words, to the presence of cholecystitis, choledochitis, and cholangitis. To the group of cholelithiasis there must be added a large class of cholecystitis without the presence of gall-stones. The symptoms are alike in both cases. The term "gall-stone colic," therefore, should be substituted for biliary colic, the colic being an expression in the majority of instances of an infectious process in the gall-bladder, and less frequently is it due to a mechanical contraction of the ducts when a stone becomes lodged within. Sufficient emphasis cannot be laid upon the fact

that all symptoms, whether they be pain and localized tenderness or the reflex gastric disturbances, all are due to the infection and inflammation in the gall-bladder or ducts.

The postoperative cases with recurrence of symptoms which very often simulate attacks of biliary colic, as if the gall-bladder with its contents had not been removed, stress the point of a persistent infection in the larger ducts and indicate that pain is not only due to mechanical factors, such as the contraction of the cystic duct incident upon the passage or impaction of a calculus, but show a disturbance in the neurogenic apparatus of the common and hepatic ducts which is brought about by the residual infectious process.

That the static gall-bladder readily becomes a target for infection has already been mentioned. A sudden jar, a blow, a fall against the gall-bladder, pressure from corsets, will facilitate bacterial invasion. Also any form of intercurrent bacterial infective disease, such as tonsillitis, puerperal infection, an acute articular rheumatism, gastro-enteritis, typhoid, and paratyphoid, can give rise to an inflammatory reaction. I have seen several instances of acute cholecystitis develop during an attack of acute articular rheumatism which followed tonsillitis or chronic antrum disease.

From the statistics of Kehr, Smithies, the Mayos, Alvarez, and others we learn of the prevalence of infected gall-bladder without the presence of stones. In an analysis of Smithies' 1000 operations for cholecystitis, we find 430, or 43 per cent., diseased gall-bladders without stones, 46 contained biliary grit, and 509 contained stones. Alvarez²⁴ reports 60 cases of cholecystectomies, out of which 33 per cent. showed the presence of stones, the remainder (67 per cent.) containing none, 82 per cent. of the calculus gall-bladders showed living bacteria, and 57 per cent. of the acalculus gall-bladders likewise showed the presence of living bacteria. Most all showed histological changes.

Often the acalculus gall-bladder may show little or no apparent gross pathological changes, and the surgeon will be confronted with great difficulty during laparotomies in deciding which gall-bladders should be removed. It falls upon them to

become thoroughly familiar with the appearance of those gall-bladders that indicate the least departure from the normal. They must take into consideration the color of the gall-bladder, the consistency of its walls, the presence of adhesions and glands, the appearance and course of the cystic duct, the condition of the pancreas and liver, so that neither unnecessary cholecystectomies may be performed, nor should a diseased gall-bladder remain behind. I have convinced myself in a number of instances that the conservatism of the surgeon in leaving an apparently healthy gall-bladder behind and removing the appendix instead, necessitated subsequent cholecystectomy for the final relief of symptoms. I often wonder how many of the so-called unsuccessful appendectomies are, in reality, cases of unrecognized chronic gall-bladder disease.

Kehr states, after an experience based on 1500 cholecystectomies, that often a normally appearing gall-bladder must be removed in the presence of definite gall-bladder symptoms.

Difficulties will be obviated when we shall all become fully aware that it is the infection and not the stone in particular we seek to eradicate in the same manner as the removal of diseased tonsils or a diseased appendix.

DIAGNOSIS

While considerable aid has been added through the visualization of the gall-bladder by the Graham and Cole method, as well as through the utilization of the Einhorn and Meltzer-Lyon tests, the diagnosis of biliary diseases must rest often on clinical data, especially on the anamnesis. Its recognition is comparatively simple when one is thoroughly familiar with the character and the location of the pains; their distribution and radiation, and all the reflex phenomena under which these conditions masquerade. It is to be remembered that frequently a functional cardiospasm may be due to a diseased gall-bladder, and that occasionally the pain may be referred to the left shoulder. Very often a simple eructation may be the only symptom. This may persist for many years unaccompanied by attacks of pain, being regarded as a gastric neurosis. The epitome of Deaver, of "fair,

fat, and forty, belching gas," still remains a classic. Difficulties are occasionally encountered when the radiation of the pain is toward the precordium or arms, simulating coronary disease. I have observed several instances in patients with anginal pains who were cured by cholecystectomy, and in 1 case, where the diagnosis of cholelithiasis was doubted, the patient some months later developed an acute gangrenous gall-bladder and died two days after the operation.

TREATMENT

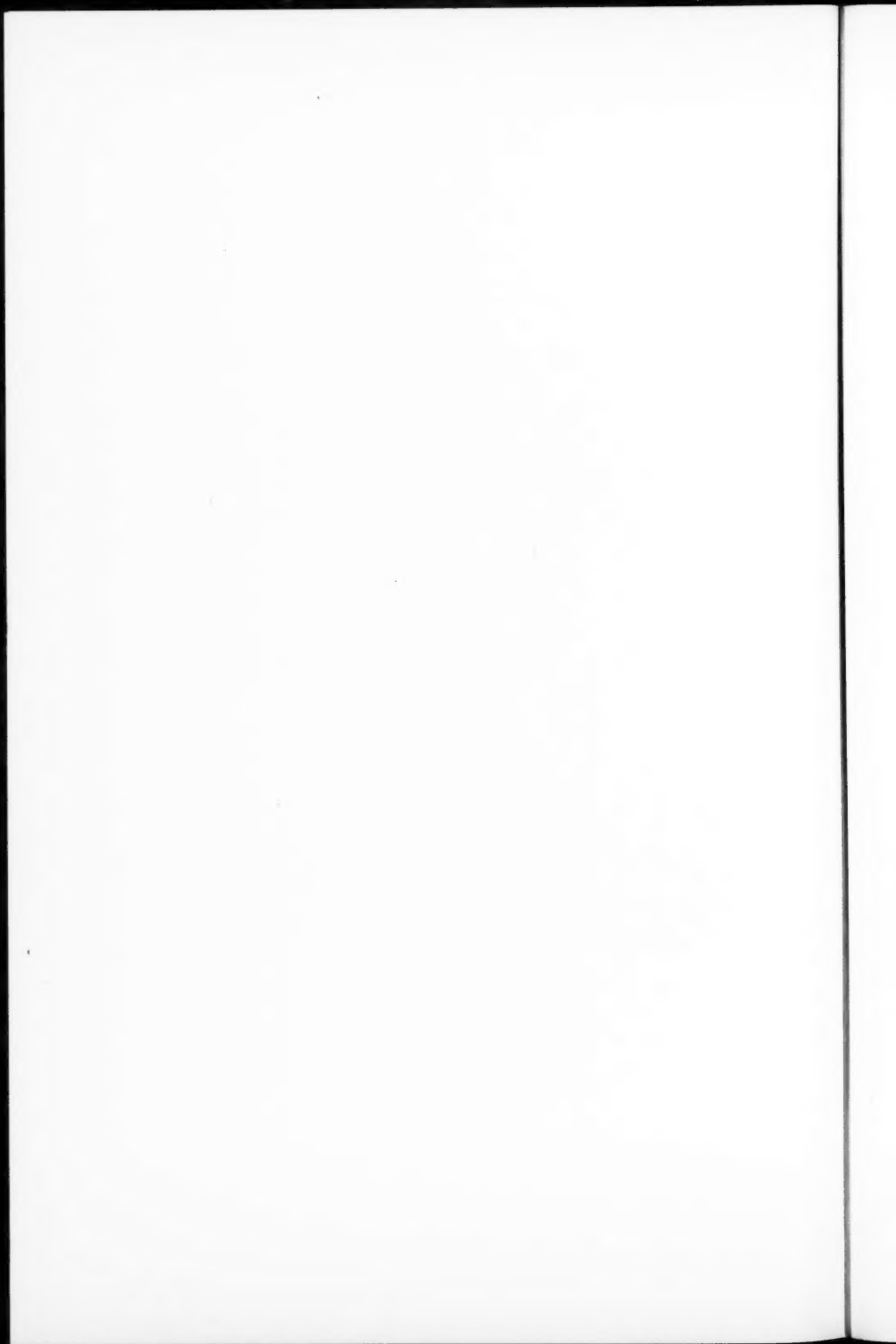
A word as to treatment: In definitely outspoken cases of biliary disease with persistent attacks cholecystectomy is the only form of treatment. Where surgical therapy is not feasible the medical indications are to correct the metabolic disturbances, to eradicate all septic foci, such as arise from tonsils, teeth, or sinus infections, dietetic and hygienic measures to prevent overloading of the gastro-intestinal tract with cellulose foods and gaseous beverages, to keep the bowels clean so as to avoid overdistention of the hepatic flexure, to promote bile drainage with various hydragogue cathartics and occasional visits to spas, and last, but not least, to prevent physical and emotional disturbances.

As to the question of gall-stone solvents, we have not as yet produced any substances that will dissolve gall-stones. While it has been shown that the desoxycholate solutions may reduce the weight of the gall-stone *in vitro*, yet *in vivo* their administration would be unfeasible and even harmful. They may split a stone and form new centers of crystallization which may add to the infection and to the pathology; therefore at the present time such substances are dangerous and are distinctly contraindicated.

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NEW YORK CITY

THE IMPORTANCE OF GASTRIC SECRETORY HYPO-FUNCTION

THE normal gastric secretion is carried on by the glands secreting (1) hydrochloric acid from the gastric cells proper and (2) the zymogens of the ferments from the chief cells of these glands and from the pyloric glands. These zymogens form (1) pepsin, the proteolytic enzyme; (2) chymosin or rennin, the casein precipitating ferment, and (3) lipase, the fat-splitting ferment.

The normal average amount of the gastric secretion in twenty-four hours is 1500 c.c. Pepsin and hydrochloric acid have a very important function, as they lead to the hydrolytic cleavage of the proteins with the formation of the soluble proteoses and peptones. Most of the proteins must first be acted on by pepsin and hydrochloric acid before the trypsin of the pancreatic juice can have any effect upon them.

The function of the hydrochloric acid is: (1) to interrupt the action of the ptylin of the salivary juice; (2) to kill bacteria; (3) to activate the zymogens to ferments; (4) to regulate the closure of the pyloric orifice, and (5) to stimulate the production of secretin in the duodenum, which substance itself on absorption increases pancreatic secretion.

The autonomic nervous system has a great influence over gastric secretion. Vagus stimulation favors hypersecretion, while, on the other hand, gastric secretion is inhibited by sympathetic nerve stimulation.

There is normally the tendency for the production of gastric secretion under the influence of appetite, mastication, and direct chemical action of certain foods on the gastric mucous membrane.

Diagnosis.—It is first essential to ascertain whether a secretory dysfunction exists. The history and physical examination cannot prove or disprove impaired secretory function. The reports of roentgenographic and fluoroscopic examinations are also not conclusive.

A single extraction from the fasting stomach or after a test-meal is not sufficient. A fractional gastric extraction and analysis carried on for at least two hours after the test-meal is necessary. This must be done in order to keep from overlooking a delayed hydrochloric acid secretion. And even then an oatmeal gruel test-meal (fractional aspiration) may not stimulate the secretion of hydrochloric acid, while a test-meal of peptone or bouillon may bring out the delayed acid secretion.

Winkelstein and Marcus,¹ in studying the excretion of the neutral red (Ehrlich) dye from the human stomach, suggest that such a procedure may prove of value in addition to the usual methods of studying the secretory function of the stomach. It seems that the ability of the gastric mucosa to excrete the dye follows the stomach's ability to secrete hydrochloric acid. After the intramuscular injection of neutral red dye it appears much more quickly in the condition of hyperchlorhydria than it does in achlorhydria. In achylia gastrica (absence of both acid and ferments) the appearance time is greatly increased, and in many instances no trace of the dye does appear in the gastric contents.

After determining the exact capability of the stomach to secrete hydrochloric acid and ferments, we may proceed to further diagnosis. In so many cases of so-called hypersecretion there is actually only a delayed emptying of the stomach which produces an apparent hyperacidity and hypersecretion. However in the condition known as Reichmann's disease, or gastrosuccorhea, there is a continuous hypersecretion and the stomach may contain from 30 to 500 c.c. of a thin, clear, watery fluid. Chemically the findings are the same as that of normal stomach juice or there may be a hyperacidity.

Hyposecretion and Achlorhydria.—Gastric symptoms are rarely present in uncomplicated cases of achlorhydria. "Heartburn" and epigastric distress usually occurs about one hour after

eating. These symptoms may be relieved by alkaline medication or food. There may be present a sort of "empty" feeling in the upper abdomen soon after eating. This sensation is caused by the rapid emptying of the stomach which is so often present in achlorhydria. Most of the symptoms present in achlorhydria are intestinal, and include diarrhea, intestinal flatulence, and discomfort.

Gastrogenous diarrhea usually results from the absence of gastric secretion, but may be associated with secretory insufficiency. The factors causing diarrhea are: (1) The food is not properly prepared in the stomach for intestinal digestion; (2) active organisms which should be destroyed in the stomach gain access to the intestine and pathological processes result. (The diarrhea and colitis in pellagra most likely result from an achylia.)

Interference with digestion applies both to proteins and carbohydrates. The connective tissue of meat-fibers remain unattacked due to the absence of hydrochloric acid, and the cellulose sheath of the vegetable fibers are imperfectly broken down. As a result of this impairment to normal digestion both fermentative and putrefactive processes occur in the intestines.

Incomplete activity or absence of gastric enzymes leads to inadequate predigestion and thereby retards or impairs the proteolytic activity of the intestinal and pancreatic juices on proteins. Putrefaction is thus increased. Poisonous disturbances resulting in the intestines lead to diarrhea, colitis, and in all probability cause deleterious effects upon the blood.

Vanderhoof² in summarizing the clinical features of diarrhea caused by the enzymatic dysfunction of the stomach, lays special stress on the morning diarrhea. The patient may awaken early and have one or two bowel movements before breakfast, and five or six before the noon meal. Sometimes these evacuations are even more frequent. As a rule they are less frequent in the afternoon and evening. Some patients may have as many as fifteen movements a day.

The stools are liquid, offensive, and alkaline in reaction. They contain undigested food, fatty acid crystals, mucus, and

sometimes blood. They are usually yellow in color and have a sour odor. The intestines are distended with gas. There is a mild griping, rumbling, and discomfort. Occasionally there is severe pain. Irritability of the urinary bladder is a frequent complication.

Evacuation gives temporary relief. Gastric symptoms may or may not be present. The gastric symptoms may resemble those of hyperchlorhydria; such symptoms occur in uncomplicated achylia.

Pernicious Anemia.—The frequency of absence of hydrochloric acid in pernicious anemia has long been recognized. At present the consensus of opinion is that the association is constant, and no case may be called pernicious anemia if hydrochloric acid is present in the gastric contents.

Achlorhydria may be found long before the blood-picture becomes diagnostic. There is usually a history of recurring attacks of gastro-intestinal upsets, especially diarrhea, with the constant absence of hydrochloric acid in the stomach contents. Finally, such symptoms develop as progressive weakness, paresthesias of the extremities, increasing pallor, and soreness of the tongue. The last and conclusive finding is the peculiar blood-picture. Some have suggested that because of the long continuance of achlorhydria before the onset of other symptoms the absence of hydrochloric acid is the real cause of pernicious anemia. It has been suggested that the lack of secretion permits passage through the stomach into the intestine of such organisms as streptococci and *Bacillus welchii* in such numbers as eventually to produce sufficient toxin to bring about hemolysis and other disturbances of blood production.

It is just as possible, however, that there may be some other toxin that first attacks the gastric mucosa and later the other structures.

Whenever persistent achlorhydria is present the case must be held under observation and must be watched for the appearance of these signs, symptoms, and the blood-picture of pernicious anemia. Pernicious anemia cannot be diagnosed unless achlorhydria is one of the constant manifestations.

Barker³ gives the most recent conception of the etiology of pernicious anemia. He says that hereditary disposition is the main factor and that various provocative factors must be present, such as poisons derived from bacteria, fungi, or animal parasites in the digestive tract.

Gastric Cancer.—Achlorhydria is not so important in the diagnosis of gastric cancer. The presence of an achlorhydria or subacidity in cancer of the stomach occurs late in the disease. By that time other factors have decided the diagnosis. The secretion of hydrochloric acid decreases as the tumor grows. The toxin produced inhibits or destroys the secreting cells and there is a resulting gastritis.

With the history of prolonged indigestion, loss of weight and strength, and increasing pallor and subacidity the diagnosis of cancer is evident. The fractional gastric analysis may show some hydrochloric acid present. The Roentgen-ray study is the most important factor in the diagnosis.

Syphilis of the Stomach.—Although syphilis of the stomach is a very rare condition, there being probably less than one to one hundred other organic lesions of the stomach, one of the most constant findings is impaired gastric secretion. There is always present a gastric subacidity, anacidity, or a complete achylia.⁴

In true gastric syphilis there must be definite syphilitic pathology, such as a tertiary lesion, especially a secondary mutilating sclerosis, gumma, or gummatous ulcer. The Wassermann reaction of the blood is positive. These cases, as a rule, respond quickly to antisyphilitic treatment.

Chronic Gastric Inflammation.—The abundance of mucus, especially in the fasting contents, and the presence of achlorhydria and sometimes of gastric retention, usually make the diagnosis of chronic gastritis.

Of course, the history is important and we find habitual indiscretion in diet as to quantity and quality. Improper mastication, overseasoning, irregular intervals between meals, and the eating of foods either too hot or too cold are the important factors. Sometimes conditions such as cirrhosis of the liver or

chronic passive congestion will produce stasis in the gastric walls, with a resulting gastritis.

The continued swallowing of infectious material from the gums, teeth, tonsils, sinuses, or trachea and bronchi may cause a gastritis.

The roentgenographic examination is negative in these cases. There is no loss of weight or strength. There is none of the anemia which characterizes a malignant condition of the stomach walls. There are none of the blood changes or paresthesias characterizing pernicious anemia.

Chronic gastritis is a common cause of hyposecretion and achlorhydria. Usually hyposecretion is the condition more commonly met.

Cholecystitis.—Von Aldor⁵ states on the basis of a large number of cases observed that in about one-half the number of cases of cholecystitis there was present a marked degree of a hypochlorhydria or an achlorhydria. Blalock⁶ reports an achlorhydria in 23 per cent. of the cases at the Johns Hopkins Hospital who had gastric analysis performed and who were operated on for chronic cholecystitis.

Cheney⁷ reports that in the wards of the Stanford Hospital during the five years from January 1, 1920 to January 1, 1925 84 patients who were operated on for gall-bladder disease (diagnosis confirmed by gross and microscopic examination of the gall-bladder) in 14 no gastric examination was made, but in the remaining 70, 37 showed either a great deficiency or a complete absence of hydrochloric acid secretion.

He discusses three different theories:

"First, it has been asserted that an activating hormone is produced in the bile tract or in the duodenum that is essential to the stimulation of secretion by the acid-forming cells of the stomach, and that this substance is destroyed by gall-bladder disease. But such a hormone has never been definitely demonstrated; gall-bladder disease does not always produce achlorhydria, and even after removal of the gall-bladder achlorhydria rarely if ever results. With regard to the last point, an interesting report was published by Dahl-Iversen in 1924, from the

Animal Physiological Institute at Copenhagen, of which Mollgaard is director. He found that in many experiments on dogs, monkeys, and rabbits removal of the gall-bladder did not seem to modify in any way the secretion of free hydrochloric acid.

"The second theory is that achlorhydria is a reflex due to the common innervation of the gall-bladder and stomach, so that what impairs the function of one impairs likewise the function of the other. The objections to this are the same as to the hormone theory, that gall-bladder disease and achlorhydria or gastric hyposecretion are not inevitable associates, and that even the removal of the gall-bladder does not inhibit gastric secretion.

"Third, the theory advanced by von Aldor, and the most likely one of all, is that chronic gastritis is associated with a certain proportion of the cases of cholecystitis, and that in these will be found not only achlorhydria, but an excess of gastric mucus that constitutes the diagnostic feature. This theory will account also for the cases showing hyposecretion without complete suppression, and will explain why many show no change in secretion simply because no chronic gastritis coexists. It will also explain the occasional case in which gastric secretion recurs after the diseased gall-bladder is removed because coincidentally the gastritis has disappeared. The general impression, however, among all observers throughout the literature reviewed is that if achlorhydria exists before removal of the gall-bladder, it persists afterward as well."

Combined Sclerosis of the Spinal Cord.—Collier⁸ describes under the title of "subacute combined degeneration of the spinal cord" a condition which is commonly known as combined sclerosis. Certain symptoms and signs are present and are exactly like ones found in pernicious anemia. There are subjective feelings, such as tingling, numbness, the feeling of pins and needles in the arms and legs, and evidence of minor loss of power. This may occur without anemia, as it does in *tabes dorsalis*, and progress to fatality without any evidence of pernicious anemia.

Collier's opinion, however, is that this type of anemia occurs

in every case of combined sclerosis, though its appearance may be delayed for years. The nerve changes and the achylia in pernicious anemia does not improve during the remission stage when the blood condition improves.

Bell and Hurst⁹ of London, in 1922 reported 10 cases of persistent achlorhydria in combined sclerosis. Vanderhoff says that every person with achlorhydria is a potential case either of subacute combined sclerosis of the spinal cord or pernicious anemia.

Neuroses.—There is a group of cases of achylia which is not explained unless by disturbance of innervation commonly described as functional. The elderly individual very often shows this condition. There is no seeming disturbance of the general health and digestion, excepting for occasional gastric discomfort or diarrhea. In this condition if the gastric motility is normal no symptoms, as a rule, occur.

Suppression of the gastric secretion, in conditions such as Glénard's disease (visceroptosis and neurasthenia), is not usually caused by the low position of the stomach, but to the faulty innervation supplying the glands. Other types of neurasthenia have been said to be responsible for impairment of the secretory function of the stomach, but every possible investigation for other causes of the absence of secretion must be made before the diagnosis of neurasthenia is accepted.

Hysteria (anorexia nervosa), with its accompanying aërophagia and globus, has disturbances of both the sensory and motor tract. The so-called gastric neuroses have more commonly a hyperacidity and a hypersecretion than a hyposecretion.

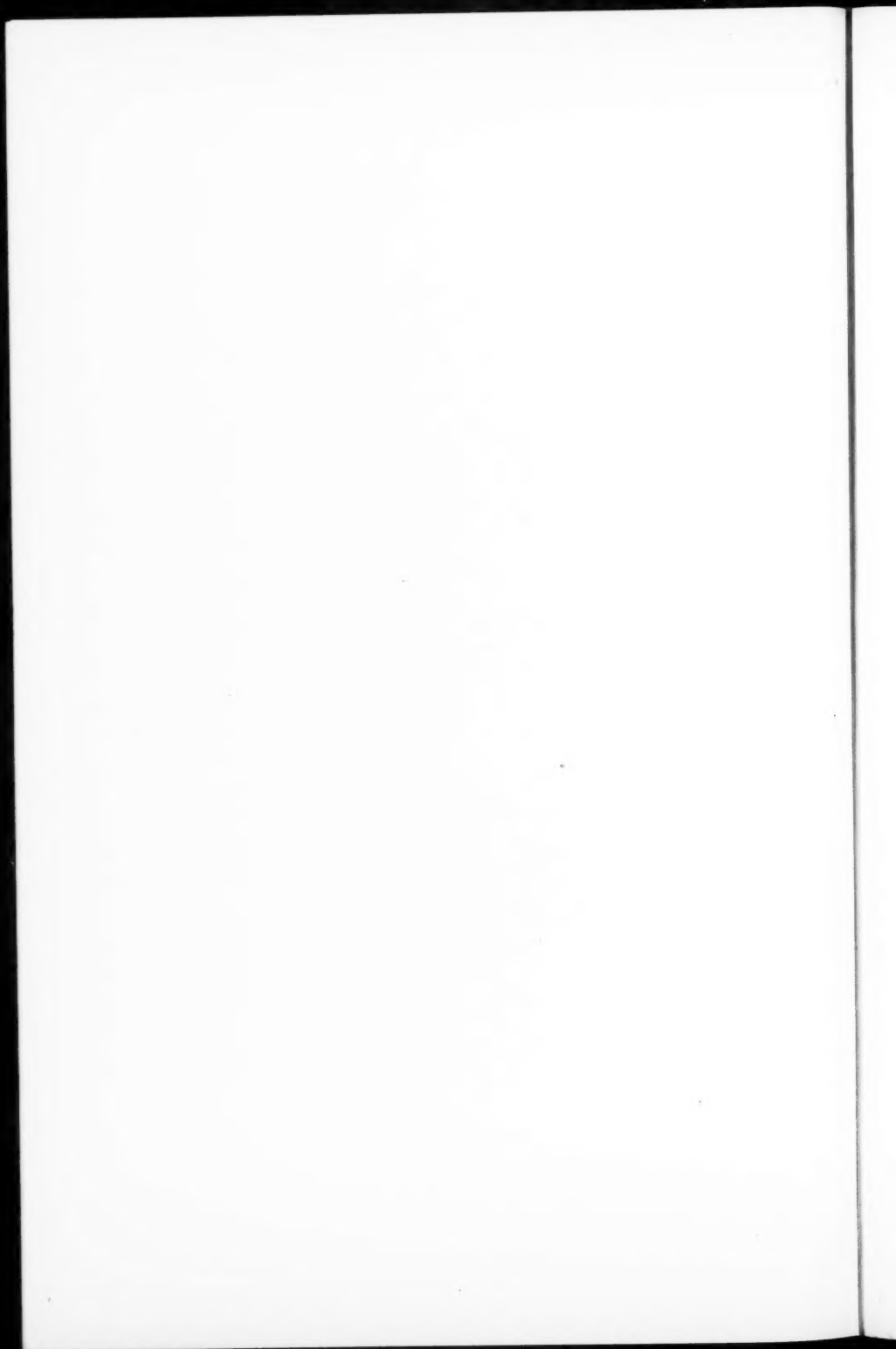
Even though achlorhydria be only functional at the onset, if it persists long enough there may develop pathologic changes of the blood and spinal cord. These changes may occur because of absorbed toxins from the intestinal tract that the presence of normal gastric secretion would have kept from developing.

Conclusions.—1. The importance of decreased gastric secretion, subacidity, or achylorhydria, in connection with several well-known diseases which are enumerated in the text, is discussed.

2. It is concluded that achlorhydria or decreased gastric acidity should be considered as diagnostic of or as a precursor of several serious conditions.

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CLINIC OF DR. HERMAN GOODMAN

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FIBROMA PENDULUM

CLINICALLY, the subject of fibroma pendulum is an interesting one. It occurs to me that a number of different conditions may be grouped under this descriptive title. Recently I have observed a number of persons with what is best described as fibroma pendulum, that is, they presented a solid or seemingly solid mass hanging from a broad pedicle from the remainder of the skin.

CASE REPORTS

At an exposition recently I examined a man whose picture is given here. He was a colored man, some thirty years of age, who gave a graphic description of his condition, and was so certain of the etiology that he warned ladies who were in a delicate condition to look the other way. It was easy enough to determine that the mass on the side of the head was a pendulous fibroma. The man also had numerous smaller solid tumors on the chest and other parts. So one had to consider that here was another example of multiple fibroma with fibroma pendulum.

The skin over the lesion was not darker than over the rest of the body. In white persons it is held that the tumor shows hyperpigmentation. The surface of the mass showed dilated follicles and gross sebaceous gland apertures. The parts were terribly distorted, so that, in truth, half of the scalp was lying about the level of the chin; the soft parts about what should have been circumorbital were down near the nares; and the corner of the mouth of the affected side was about at the level of the thyroid cartilage. The entire mass was movable, and it could be lifted

to show the under surface. The mouth could be opened on the non-affected side only. Sensation was said to be normal. Sight from the eye on the affected side was gone.

The condition was reported to have been present since birth and to have progressed with the years.



Fig. 134.—Bingo, found in the wilderness of Virginia.

Within a few weeks after seeing the gentleman described above I saw a man with a very similar lesion on the cheek. He was a white man, Jewish, about thirty-five years of age. The mass had been present since childhood, and had increased in size. Several attempts at removal had been futile. He promised to send me photographs of various phases of his condition, but has not done so. The pendulous tumor in this man had its

upper limit about at the middle of the cheek. The mass hung low enough as to be included within an especially large collar to rest on the chest wall. This mass was much darker than the skin of the man, and the scars of his various operations were visible.

Recently, too, I had the opportunity of seeing a patient of Dr. Willy Herbert Meyer whom he has shown about town at various societies under the title of diffuse fibroma of the eyelid and cheek. Dr. Meyer will undoubtedly report his case in full.

A survey of my previous cases reveals that numerous patients have been seen at one time or another with individual lesions which might be called fibroma pendulum, usually associated with other tumor growths. I have no photographs to show of these patients. Consulting the text-books on hand shows a good picture in Ormsby (2d ed., p. 562). I recall an old Jewish gentleman seen years ago with a tumor mass similar to this. The picture in Pusey (4th ed., p. 1013), accredited to F. G. Harris, is a milder example of the type of tumor which is illustrated herewith (Fig. 134).

The relationship between fibroma pendulum and what has been regarded as dermatolysis of the partial or circumscribed form is obscure. In this connection it might be well to review a case of accepted dermatolysis recently seen and a report of which has appeared in *Surgery, Gynecology, and Obstetrics* (with E. Traub), January, 1926.

CASE REPORT—DERMATOLYSIS

Miss F. F., an American born school girl fifteen years of age, first presented herself to the Clinic of the New York Skin and Cancer Hospital August 13, 1924. Her family history was negative, except that a sister had had an erythematous eruption, probably toxic in nature, which disappeared spontaneously. Her past history had no bearing on the condition presented. As far back as the patient or her parents remembered, probably from earliest childhood, a small spot had been noticed in the center of the back of the neck just below the hair margin. This lesion had gradually increased in size, slowly at first, apparently more rapidly within the past year. She now presented a slightly raised

pendulous area of skin on the nape of the neck measuring $2\frac{1}{2}$ by $1\frac{1}{8}$ inches, the long axis of which was parallel to the long axis of the vertebral column. The follicular openings in this area were enlarged, but the hair was fine and sparse. The skin was lax, the natural folds and rugæ enlarged, giving rise to an uneven surface which was slightly more pigmented than the surrounding integument. The skin could not be drawn out further than its redundancy permitted. The patient had no other skin abnormalities.

The patient's general health was good. The neurologic examination revealed nothing abnormal, and the patient had kept up with her classes at school. She was apparently of average mentality.

The lesion was removed under local anesthesia by Dr. William Asbury Smith (now of Beaumont, Texas) and the wound healed, resulting in a linear scar.

The histologic features of partial dermatolysis are hypertrophy of all portions of the skin, especially an increase in the fibrous bundles. The subcutaneous tissue shares in the general hypertrophy.

There is no tendency to spontaneous involution. Treatment is purely surgical. There is no tendency to recurrence.

HISTOLOGY OF DERMATOLYSIS

Examination of prepared sections of the case of partial dermatolysis revealed that the greatest abnormality existed in the derma. The tissue was in cross-section, longitudinal, and irregular. Clear areas of edema were interspersed between layers of fibrous tissue. Nuclei were sparse compared to the number of fibers. Numerous small capillaries were seen with normal walls. The lumen of the capillaries were dilated, but empty of cellular content. Branching of some of the capillaries was seen.

The hair-follicles and sebaceous glands present were broadened and somewhat lengthened.

Several islands of epidermic cells were present in the derma. No connection with the epidermis was found in the section studies. These were part of the lanugo hairs.

The papillary bodies were insignificant. Along most of the section the papillary bodies were irregular.

The line between the derma and epidermis was demarcated by a line of hyperemic, vacuolated cells of pigmented basal layer.

The epidermis was thinned. The prolongations down of the pegs were irregular, sometimes branched. The surface was in distinct folds. The horny layer was adherent within the folds and filled the pits. Over the hair-follicle the surface was indented and filled with a veritable keratotic plug. The summits of the folds were practically free of horny layer cells. The keratinization was normal.

The malpighian layer was much thinned, varying from 5 to 10 cells thick. The cells were rather closely packed without much separation of the prickles. There was a clear space about some of the nuclei.

The cells of the basal layer were swollen. The cell protoplasm was almost ballooned with fluid, and the nuclei sometimes were to one side and sometimes in the middle. The pigment granules were restricted to the basal layer cells, but the pigmentation was distinctly increased.

There was little subderma present in the section. It showed dilated vessels of normal thickness. The sweat-glands were of normal appearance.

The Weigert elastic tissue stained sections showed the elastic fibers directly beneath the basal cell layer to be practically continuous. The fibers were thicker than normal, curled, branched. Other elastic tissue fibers seemed crumbled. In the derma proper the amount of elastic tissue fibers seemed small. The circum-vascular elastic fibers were normal in thickness. In the neighborhood of the hair-follicles and sebaceous glands the elastic fibers were more numerous.

DIFFERENTIAL DIAGNOSIS

Cutis pendulum has been accepted by some as a synonym for fibroma pendulum, and the first has been regarded as dermatolysis. The descriptions given in the text-books for one would seem to fit the other. It will ultimately be a matter of hair splitting as in

so many other dermatologic subjects. In another communication of dermatolysis I gave the following description of that condition. Reviewing fibroma pendulum, it would seem that it cannot be improved upon for the clinical picture, but later I will mention what I regard, for the moment, as the point of departure.

The affected area of skin in dermatolysis hangs in loose folds or is sufficiently elastic to allow of stretching. The appearance of the surface of the integument may be normal, hyperpigmented, with dilated and gaping follicles or comedones. The skin is usually thickened, but exceptionally is thinner than normal. On palpation, one gets a doughy or velvety soft feel of a greasy uneven surface. The sensation may be unaffected or hypersensitive. There are no subjective symptoms. Although any part of the body may be affected, the locations most frequently involved are the face, especially the eyelids, the neck, the abdomen, and the genital region. The condition is somewhat progressive. After reaching a certain stage of development it may remain stationary.

The etiology is unknown. In certain instances the condition is congenital, in others hereditary (several generations), but usually it is acquired. The starting-point may be the site of former trauma, and the vague term of "trophoneurosis" has been applied to the causation of partial dermatolysis.

Other diseases which may be confused with fibroma pendulum include the diffuse dermatolysis or cutis hyperplastica. The "elastic skin" of the india-rubber man of the circus side show is an excellent example of this form of dermatolysis. Here the integument is generally loosely attached to the subcutaneous tissue and has the property of great distensibility occurring normally in the young of certain animals, as kittens. Diffuse dermatolysis has been studied by a number of observers.

Fibroma pendulum must not be confused with the relaxation of the skin and subcutaneous tissues encountered in senility and after pregnancy. In both of these the hypertrophy of the constituents of the skin is lacking. Nevi and sebaceous cysts are readily distinguished. Lipoma and lipomatosis may be recognized. The form of lipomatosis known as Dercum's disease would be readily distinguished. The relaxation or hanging in

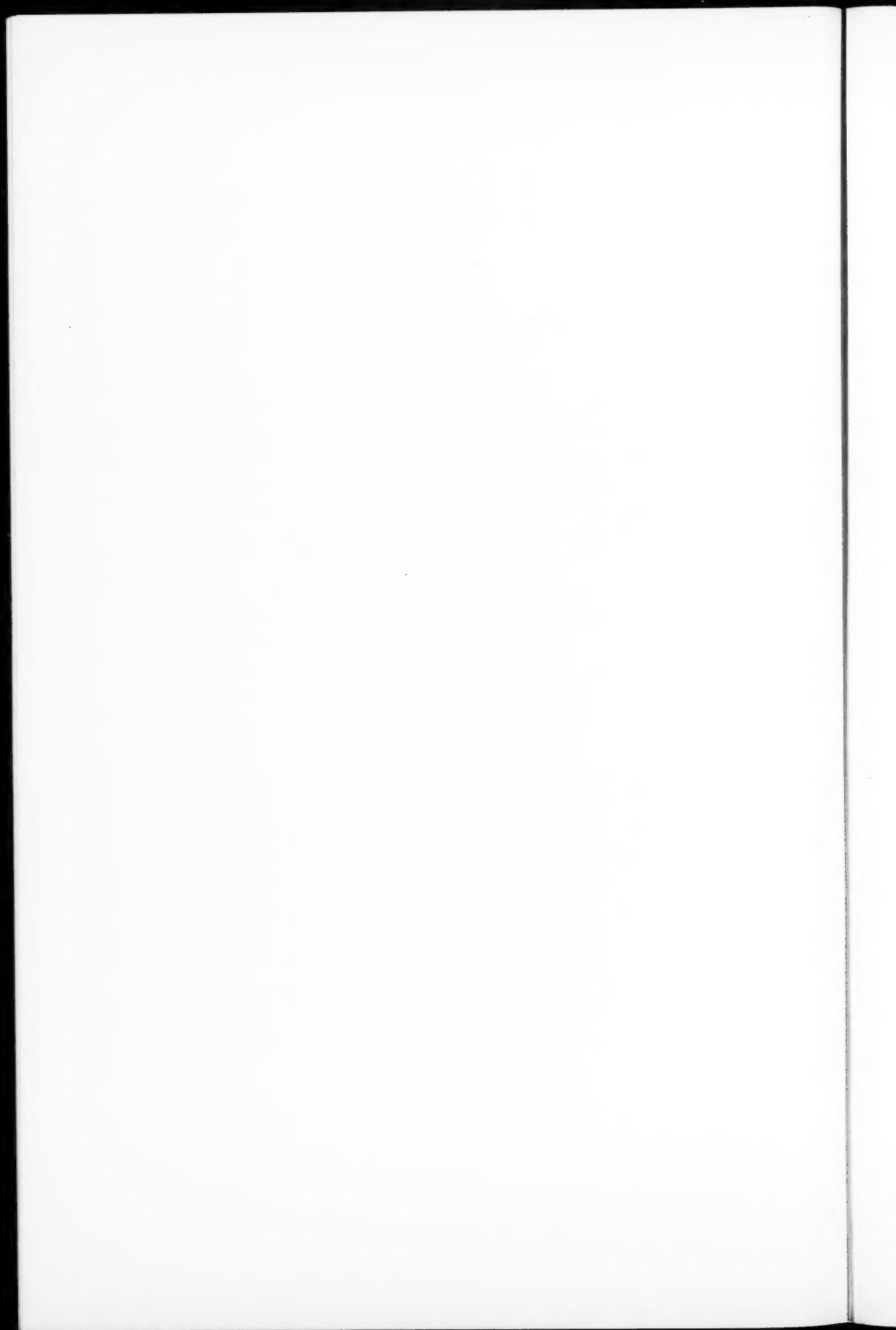
folds of the skin are features of pseudoxanthoma elasticum, but associated papules and flat plaques of the proper coloration are absent in fibroma pendulum.

COMMENT

For the time being I am of the opinion that circumscribed dermatolysis could be differentiated from fibroma pendulum by the fact that it is not preceded by any definite tumors. The fact that in some instances such evident tumor diseases as Recklinghausen's disease, multiple fibromas, and the depressible fibrous tumors associated with the disease known as benign multiple new growths of Schweniger-Buzzi show one or more masses which hang in the same manner as fibroma pendulum, would indicate that it is not possible to say definitely that fibroma pendulum is a disease *sui generis*. The side show individual whose picture is shown presented discrete fibromatosis; the patient of Meyer also showed additional tumors (as well as other defects), but the girl previously reported as partial or circumscribed dermatolysis had no other skin tumor.

I believe it is proper at this time to mention that there has been a great confusion between multiple fibromatosis of the skin and the neurofibromas. I believe that multiple fibromatosis is not associated with nerve-fibers. Competent pathologists have not found any particle of nerve-fiber in multiple fibromas of the skin. In neurofibromatosis the tumors are usually along nerve trunks, are subcutaneous, and have been described to include portions of nerve endings. In my opinion only tumors of the multiple fibroma type may become pendulous and assume the fibroma pendulum form. Although I have seen a great number of what I have decided to be neurofibromas, no tumor of that group has shown any evidence of becoming pendulous.

The purpose of this presentation has been filled if it calls attention to fibroma pendulum; its possible association with other fibromas; its non-identity with dermatolysis, and its occurrence or the occurrence of similar lesions in other diseases, as in multiple fibromas of the skin, which I contend are very different from neurofibromas.



CLINIC OF DR. ARTHUR F. KRAETZER

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NEURASTHENIA

MARK TWAIN said that everybody talks about the weather, but nobody ever does anything about it. With considerable truth the same can be said about neurasthenia. Orthodox medicine is just beginning to inculcate a true understanding of it. The various cults—osteopathy, chiropractic, physical culture, Christian Science, vegetarianism, and so on down the line—have completely failed, despite their noisy arrogations of omniscience. That the cults should fail is not surprising to anybody with a modicum of information about anatomy and physiology. I have performed a fair number of autopsies on the spinal cord, and to produce any impression upon the vertebræ, even with knife and saw, chisel and hammer, is a tough, tedious, and perspiration-producing job. To claim that a chiropractor, with a thrust of the heel of his hand, can move one of these same vertebræ, and, furthermore, move it with precision and finesse, is going just a bit too strong. Furthermore, the fundamental theory of chiropractic, that disease is due to the pressure of misplaced vertebræ on spinal nerves, is absurd, because any such pressure would first betray itself by fiendish pain. As for Christian Science, a "cure" in this field is simply the substitution of one hysteria for another, the substitution of a more comfortable abnormal mental state for a less comfortable one. Abolish symptoms at times, perhaps, yes. But cure, no.

The first and main trouble is that no one has ever clearly defined what neurasthenia is. Ethmologically it means weakness of the nerves. This is absurd. Nerves are neither weak nor strong. To use such an expression is to use a figure of speech

which has no basis in reality. The creation of this term, "neurasthenia," was a great mistake. It was probably the unconscious expression of ancient animistic concepts, many of which have filtered into modern medicine. I will speak of another of these weird survivals later. To go back to neurasthenia, my own belief is that, in the strict sense of the word, there "just ain't no such animal." There is, however, a type of patient to whom the term "neurasthenia," is always and most unjustly applied. It may be best to describe a case: She was a pale, thin, sallow, intimidated woman of thirty-seven. She was afraid to ride in the subway. Going up stairs made her fear heart failure. She was utterly weary, despondent and apprehensive, unable to work, unable to be happy, unable to create anything but unhappiness in her family. Her husband had been told that she had neurasthenia, and this with a certain air, as if something really valuable had been imparted in such a diagnosis, as if the disease were the result of a certain "innate cussedness" on the patient's part, something that might be disciplined away, but which was not amenable to scientific medical care. As a matter of fact, she was sick, physically sick, and after two months of treatment along conventional medical and surgical lines was well, strong, and happy, and all this without any nonsensical admonitions to lift herself up by her own toes by "kidding" herself into believing that every day in every way she was getting better and better and better. The old, old line of "get something to occupy your mind" did not apply here. She had a working man for a husband, 3 children, and no servant. She had plenty to occupy her mind. Nor was it lack of courage, a failure to come up to the moral scratch. She had plenty of courage, for under my orders she went through two painful ordeals—the removal of diseased tonsils and horribly infected teeth—and followed a rigid diet without a whimper. She was simply sick.

Now it is this type of case, the nervous run-down woman, the tired jumpy business man, that flocks to the irregular cults for care. And I think that it is the fault of ourselves, the regular practitioners, that such is the case. Medicine makes a mistake in giving impressive names to symptoms. Nomenclature has an

insidious psychologic momentum. Once dignify a phenomenon with a name, and you forget that it is a phenomenon, a mere expression of something deeper, and come to think of it as an entity in itself. What is purely a "symptom" becomes elevated to the spurious rank of a "disease," and from then on clear understanding of it is hopelessly forestalled.

Another reason that this type of patient is badly treated is the lack of definiteness of symptoms. A patient comes into the office and all that he can say is that he "feels rotten." The routine cross-examination brings nothing to light. The temperature, pulse, heart, lungs, etc., are normal, the eliminative functions are diurnally regular, and the long-suffering doctor says, "Good Lord! How can I render a verdict and lay out treatment on such evidence? For my sins, it's another neurasthenic." So he reassures the patient, tells him that everything will be all right, and not to worry. The patient goes off to the osteopath. Now the osteopath has one strong point, and that is the assuredness of ignorance. There is a difference, however, between being ignorant of certain things, on the one hand, and knowing things that do not exist, on the other. The osteopath knows things that are not so, and he tells his patients a lot of absurdities with a confounded air of finality that unquestionably conveys a certain moral buck-up. I once visited an osteopath myself under the following circumstances: A patient of mine was a great believer in the cult. Just why he came to me I do not know, except that we were good friends. His favorite amusement was to tell me how deficient the doctors were, and how marvelous the osteopaths were, particularly his own. I said to him, "Can he cure my cold?" "He certainly can." "Well," I said, "I'll take you on. What's more, I'll tell him I'm a doctor and play perfectly square with him." I went. The osteopath laid me on a table, stretched my joints to the limit of their capacity, cracked my neck, and then, without warning, gave me three sudden and violent pokes in the region of my appendix. He turned to me very gravely and said, "Your portal vein is congested, and if you don't have it fixed you'll lose your memory and your power of concentration." When I got back my breath, I gasped, "How could you tell?"

He replied, with oracular finality, "I felt it." Now the portal vein is about 6 inches north of where he poked, and furthermore, is absolutely inaccessible to palpation. No touch, even the most delicate, could ever detect it. And, you will remember, the osteopaths boast of their very expert knowledge of anatomy. My cold, incidentally, ran its usual ten days.

But to go back to our patient whose sole complaint was "feeling rotten." The main thing to remember is that symptoms, *i. e.*, the subjective complaints of the patient, are, in general, ambiguous. Modern scientific diagnosis is not based on symptoms, but on the objective findings which the doctor's technical skill brings to light. A stomach-ache may mean anything. If, in addition, there are fever, rise of pulse, tenderness over McBurney's point, and leukocytosis, it means acute appendicitis and the urgent need of speedy operation. This differentiation of subjective symptoms and objective findings is probably the one fundamental keynote of modern medical philosophy. It displaces the happy-go-lucky methods of the past with the ever-more precise methods of the future. All this is quite obvious to men of modern training. What is not generally recognized, however, is that the so-called neurasthenic also shows definite objective findings quite independent of his subjective symptoms.

The first thing to realize about the neurasthenic is that *he is sick*, and he is sick in ways that by their very nature he cannot put into words. The question to ask is not "What does he tell us?" but "What does he show?" He will tell an extraordinary number of things. He will show very few things, but these few things are capable of expressing themselves in innumerable ways. And here we must go further than accepting the obvious fact that the symptom is inconstant. We must realize that the disease itself is inconstant, and is not an entity, but is rather the resultant of the interplay of numerous complex variables, one of which is the patient himself. We must endeavor to ascertain: (1) What the patient shows in the line of altered and infected structures, *i. e.*, in pathology, and (2) what the patient *is*, *i. e.*, what is the essential nature of that more or less metaphysical concept, his constitution. Under the first head we have made consider-

able advances, although it is not generally appreciated that these advances can also be applied in the case of the so-called neurasthenic. Under the second head we are merely groping. Nevertheless, in this most difficult and vital field, the beginnings are being made in the anthropometric study of the individual himself. The disease is really the algebraic sum of what the patient *has*, in pathology, and what the patient *is*, in constitution. The neurasthenic will always show definite evidence of pathology. In addition, he may or may not possess constitutional defects. These last, however, we are not yet in a position to define. That belongs to the future, and it will be a magnificent and profitable field for research. It belongs, in part, to the field of the endocrine glands, about which such beautiful romance is being written today. It will not do, however, to scoff too severely at those who are overenthusiastic about the glands of internal secretion. They are in a position really quite analogous to that of the alchemists of the Middle Ages. The latter, to be sure, spun some very absurd and extravagant theories, but, on the other hand, they did one thing of supreme value, they made observations, and observations are the essential preliminary to the true theory that is formulated later.

The constitution of the neurasthenic I will say very little about, for the very good reason that we know so little about it, and for the further good reason that in the majority of cases we have no reason to suspect that his constitution differs from that of the normal individual. Right or wrong, this is a much fairer and more helpful attitude than to assume at the start that he is fundamentally different from ordinary folks, a sort of physiologic pariah who is beyond help and probably doesn't deserve it anyway. I suspect that there is a certain unconscious resentment against the inconvenient devil who baffles us. Certainly we feel more kindly toward the patient with whom we are brilliantly successful. I hope to show that it is quite possible to be equally successful with many of the so-called neurasthenics.

There is another psychological hazard that thwarts this type of case. He is not alarming, nor is he spectacular. The human mind has a curious child-like love of wonders. For this reason

the "interesting case" is some exotic rarity. This type of case generally diagnoses itself, but it can always count on elaborate study. The hospital intern, who in a year will be out in practice, is early affected by this attitude, with pernicious results. The paradox of the situation is that it is the neurasthenic who can be helped by thorough study and cannot be helped without it. The young physician is apt to develop an attitude toward him that is almost up-stage, or else gets the habit of throwing up his hands in despair when faced by this type of case.

I will say very little about the symptoms, or subjective complaints, of the neurasthenic. They are many and varied, and there is little profit in doing more than listing them. They are: easy fatigue, "nervousness," lack of "pep," vague headache, generally in the back of the head and neck, sundry ill-defined aches, generally referred to as rheumatic, tendency to faint easily, feeling "rotten," feeling "stale," compulsive fears, anxiety states, and so on. Two patients had what they described as a "nervous feeling in their wrists." Curiously enough, both of these patients had an extraordinary resemblance to each other in physique and complexion—they were both short, wiry, dark, and hairy, the so-called adrenal type—suggesting that similarity of constitution might be involved, with a concomitant similarity of symptoms. The above symptoms may show themselves in all grades and combinations. Often they result in life being hardly worth the living not only for the patient himself but also for his family.

The study of the neurasthenic must be along precisely the same meticulous lines that are followed in the case of the more obviously menacing diseases, for all too frequently some of the latter are actually present. A *complete* history must be taken, *i. e.*, a questionnaire not limited to the presenting symptom, but including every phase of the patient's past and present. Tuberculosis, in particular, must be ruled out. Persistent fatigue, being chronically "run-down," the presence of a chronic cough or frequent colds, increase the odds in favor of the presence of tuberculosis, and the patient must be assumed guilty until the most rigid investigation proves him innocent. If the question-

naire reminds him of a long-forgotten spitting of blood or an attack of pleurisy with effusion, then tuberculosis is certainly present. The tragedy of lost opportunity due to the failure to appreciate these simple facts is simply heart-breaking. Syphilis also must be ruled out, not on the basis of æsthetic distaste for the idea, but on the basis of thorough scientific study. It is extraordinarily frequent, and it can masquerade itself as neurasthenia just as it can masquerade as practically any condition. The wisdom of the routine Wassermann test cannot be over-emphasized. If the idea is offensive, then so much the worse for us. We cannot practice medicine, or build bridges, or train rabbits by being nice and kind and polite, but only by working hard and following the rules of the game. After the history must come a thorough physical examination and an irreducible minimum of laboratory work, urinalysis, blood-count, and the aforementioned Wassermann. Such an investigation, if correctly done, constitutes a really good bit of medical work that any man can be proud of. It will frequently lead directly to the diagnosis. If not, it will generally point the way to a sensible selection of special consultation or other investigation. Frequently it will entirely fail to bring to light the data needed for diagnosis, but in such an event, it will be the fault not of the doctor, but of the fundamental limitations of medical science. The man to do this work is the much-abused and all too deprecated general practitioner. He holds a position of untold strategic value. It is he who has the "first crack" at the incipient case of tuberculosis, at the incipency of everything. He must train his patients, he must discipline them, he must rule them with a rod of iron, and force them to submit to the tediousness and expense of thorough work. And he must train and discipline himself. If he hasn't the time, he must find it, or he must send his obscure cases to someone who has. But always must there be *one man* to take the responsibility, to face the music in case of failure. For it is only from the stimulus of having the interests of the patient vitally at heart that good medical work can be done. Call in specialists, by all means, but always must it be *one doctor's* responsibility. It is the fundamental fallacy of group

medicine, of commercial routine diagnostic mills, that it is so difficult to focus such responsibility on an individual.

To return to our neurasthenic. Assuming that the acutely menacing ills have been ruled out, what do we generally find in him? We are particularly apt, if we look for them, to find (1) intestinal toxemia, or so-called auto-intoxication, and (2) focal infection, *i. e.*, the implantation and growth of germs in parts of the body of such anatomic structure that drainage of the infection to the surface, with consequent healing, is precluded. The favorite sites of such infection are the roots of the teeth, the tonsils, and the sinuses, and the architecture of these parts is such that the infection is corked in tight and cannot get out. The poison from such infection seeps constantly in small doses into the blood, causing damage in distant parts of the body, particularly in the joints and ligaments, and quite possibly is responsible in a good many cases for the degenerative diseases of the heart, arteries, kidneys, etc. A point of prime importance about these focal infections is that they do not cause local pain, and, as a result, it is the devil's own job to persuade a patient to sacrifice chronically infected teeth or tonsils that to the medical eye are obvious sources of potential impairment. He invariably says, "But, doctor, I never have a tooth-ache," or "Doctor, I never have a sore throat." The point that must be explained to the patient is that to have tooth-ache or sore throat you must have not a chronic, but an acute, infection, with active proliferation of bacteria and consequent pus and pain-producing tension. The chronic infection is insidious and treacherous, working silently in the dark. The bacterial growth is too sluggish to produce local tension and pain, but it produces a constant output of poison which localizes in other parts of the body. This is the best answer to the patient's argument, "How can infection in a tooth cause pain in my knees, if it doesn't cause pain in the tooth itself?" It seems to take a considerable amount of intelligence and imagination to grasp this very simple point. Furthermore, the patient must be taught that focal infection may not give rise to pain in distal parts at all, but may simply cause a vague general feeling of unfitness and nervousness, neurasthenia, in other words.

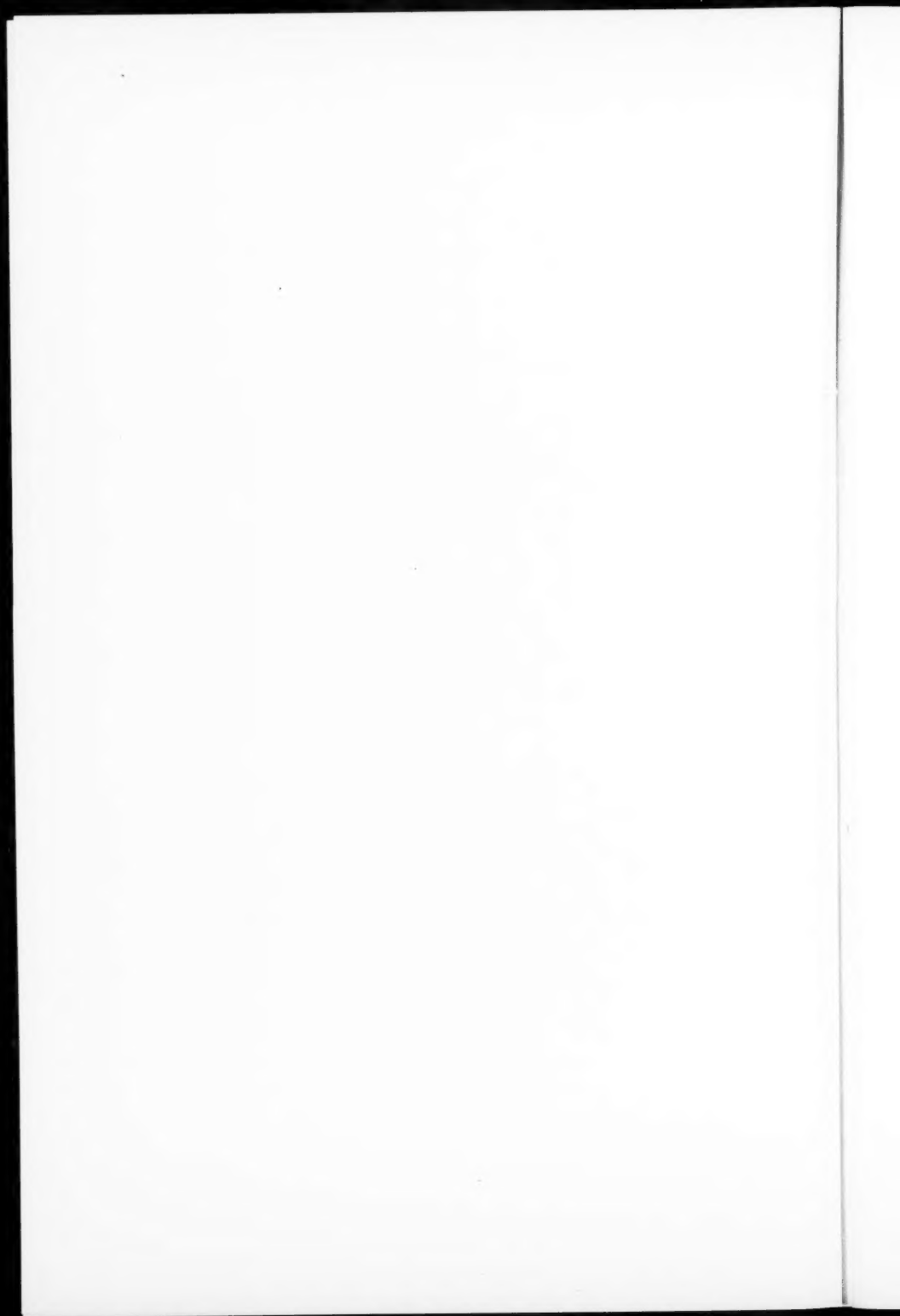
The only thing to do in these cases is to clean house, *i. e.*, remove all infection. Of course, this does not guarantee a cure. There may be other, undiscovered causes at work. But it succeeds in a vast number of cases, and is much more likely to succeed than dosing with drugs. In a case of insomnia, for example, it is much more sensible to get the body clean—which is what the removal of infection means—than to saturate the system with bromids, a most pernicious drug when taken over long periods of time. Of course, there are countless patients who prefer the path of least resistance. This moral defect is generally accompanied by a corresponding intellectual hiatus, a child-like faith in the almost sacramental value of the medicine bottle. As a matter of fact, there are about a dozen drugs on whose effect we can really count, and without which we cannot get along. There are several thousand in the pharmacopœia. An old friend of mine, a good fellow, but an awful ass—I shall see to it that he reads these words—has two badly infected teeth, and is half-crippled with a chronic back-ache. I have urged him to have the teeth removed, first with arguments, then with pleading, lastly with profanity. This being an age of equality, however, when the untrained opinion is as good as the expert, he has decided that they are his teeth, and he knows more about them than anybody else. His argument is that there *must* be some medicine for this condition, a pretty and child-like faith for those whose mental age still permits them to believe in Santa Claus. I have been looking for some such medicine for a long time, without success. At any rate, he is going to keep his teeth. The odds are that he will also keep his back-ache.

The subject of intestinal toxemia, incorrectly termed “auto-intoxication,” is one on which there is considerable misunderstanding. The general belief, which is reinforced by the physical culture magazines and nature cults, is that it is due to meat, and that it can be cured by a diet limited to fruit, nuts, and vegetables. Nothing could be more erroneous, for most cases of intestinal toxemia are due not to the putrefaction of meat, but to the fermentation of starch and sugar. This prejudice against meat cannot be explained on any rational basis. It sounds more

like some semimystical tribal tabu. The upper part of the intestinal tract is reasonably clean, but the lower part, the colon, is full of bacteria. Normally, starch should be completely digested, *i. e.*, converted into a soluble sugar, in the upper intestine, and there absorbed into the blood-stream, that is to say, side-tracked out of the intestinal canal. If such digestion and absorption do not take place, then starch actually gets into the bacteria-infested colon, and there ensues exactly what happens when starch is added to home-brew, namely, fermentation, with the formation of gas and poisonous products, absorption of which causes a whole train of symptoms, chiefly nervousness, easy fatigue, and general wretchedness. The same statement applies with even greater force to sugar itself. Small amounts of this substance can be side-tracked high up in the intestine and prevented from reaching the colon. If inordinate amounts are taken, however, fermentation is bound to occur, with resulting trouble. There are very few individuals who do not eat an inordinate amount of sugar. A century ago the annual per capita consumption was 5 pounds, fifty years ago it was 25 pounds, today it is over 102 pounds. This is unquestionably one of the reasons why Americans have the worst complexions in the world. The great majority of people with acne show a carbohydrate fermentation. These cases show a characteristic tongue which can be easily recognized, sometimes coated, sometimes glazed, and always indentated along the edges by the teeth. Diurnal regularity of the bowels may cause deception and give rise to the mistaken belief that constipation is not present. That such elimination is by no means complete can be readily demonstrated by a correctly administered colonic lavage, which, by the way, is a useful help in treatment though by no means a cure. Frank constipation, however, is frequently present, and as a result we have become a nation of cathartic users, a drug habit more pernicious in the aggregate than morphin and heroin. The logical treatment is to starve out the fermentative bacteria in the colon by depriving them of the starch and sugar necessary for their growth and activity. Vegetarianism is not only useless, but is actually harmful. Fruit and nuts carry unabsorbed starch

and sugar direct to the colon, and, upsetting as it sounds, must be strictly avoided. Sugar, cereals, and potatoes must be cut out, and bread must be strictly limited. The diet must consist of meat, fish, eggs, milk, and greens. Of course, this must be passed on by the physician, who makes sure of the ability of the kidney to eliminate the end-products of protein. If constipation is present, bran, mineral oil, and plenty of water are indicated. Agar is probably just as good a bacterial culture-medium in the colon as it is in a Petri dish. Cathartics must be strictly avoided. It is, of course, implied that the aforementioned clinical study has ruled out the presence of chronic abdominal disease such as appendicitis or cholecystitis. These ideas on diet may sound very revolutionary, but they are true. That they are far from being accepted is manifest from the popularity of the candy stores and cathartic venders. A favorite argument in favor of fruit is that it overcomes constipation. Quite true, but it does so by stimulating a low-grade fermentative activity, a process which is anything but physiologic. Furthermore, its after-effect is to increase the spasticity of the lower intestine and thus restore the condition of constipation. Small amounts of fresh orange or grape-fruit juice, without the pulp, will supply the needed vitamins. Fruit in moderation is all right for healthy people, but not for the subjects of carbohydrate fermentation, which is what so many of our neurasthenics suffer from. It is enlightening but saddening to wander into a vegetarian restaurant and note the tired nervous aspects and the pasty pimply complexions.

The neurasthenic is a pathetic and tragic figure. Very often his condition is due to very simple and, to the doctor, very obvious intoxications. He must be schooled to grasp the reality of these facts, so that he will be able to understand the advice his physician gives him.



CLINIC OF DR. J. EPSTEIN

FROM THE PEDIATRIC CLINIC, BETH ISRAEL HOSPITAL

THE EVOLUTION OF THE HEART AND ITS RELATION TO THE CARDIOLOGY OF CHILDREN

A KNOWLEDGE of the child's heart implies a knowledge of the infantile and fetal heart. To understand the disorders of the heart in early life the developmental peculiarities of the heart must be known. Since physiologic functions are based on anatomic structures, a brief outline of the evolutionary changes in the anatomy and physiology of the heart will be helpful to a clearer evaluation of the structural and functional circulatory abnormalities of the young heart.

The mammalian heart is made up of a specialized muscle tissue of mesodermic origin. It appears early during embryonal development as two independent tubes which later fuse together, forming a two-chambered heart. Through a process of alteration, subdivision, and septum formation a four-chambered heart is constructed, with two of its chambers in communication through the foramen ovale and the other two through the ductus arteriosus. With the completion of the fetal heart its incessant work begins the moment a subtle stimulus sets it in motion. In the vascular system, besides various devious channels, there is the sinus venosus, the ductus venosus, and the ductus arteriosus to serve in the circulation of intra-uterine life. The incoming and outgoing blood-vessels soon join their respective auricles and ventricles, completing the early cardiovascular system, ready to propel the newly formed blood. The heart begins its career as a myogenic mechanism and the nervous control does not assert itself till a later period.

At this stage of fetal development the cardiac cells have already acquired their functional activities of rhythmicity, irritability, conductivity, contractility, and tonicity. A regional division of labor is early established with the venous cardiac end predominating in the function of rhythmicity and the arterial part in the property of conductivity. The intracardiac pressure of the right side is greater than of the left side during fetal life. This greater right-sided intracardiac pressure is necessary to the dynamics of the fetal circulation.

At birth a new order of circulatory supply and demand begins. The heart which was intended to serve a fetal circulation is suddenly called upon to change its anatomic and functional arrangements to conform to the new requirements of extra-uterine life. This is brought about by a physiologic occlusion, aided by blood-pressure changes, followed by an anatomic obliteration of the umbilical vessels, the ductus arteriosus, the ductus venosus, the sinus venosus, and the foramen ovale. While the physiologic changes in the circulation take place immediately after birth, some of the fetal anatomic structures may persist for days, months, or even years and give rise to various congenital cardiac anomalies. With the establishment of extra-uterine life the left intracardiac pressure becomes greater than the right because the left side of the heart has to meet greater circulatory demands over a larger territory than the right side.

The weight of the heart immediately after birth is about 25 grams and is relatively larger than at any other period of life. The walls of both ventricles are almost of the same thickness and the capacity of the auricles and ventricles are about equal.

With the growth of the child greater demands are made upon the cardiovascular system. To meet these demands the weight of the heart is doubled at two years of life, tripled at four years, and gradually increases in size till puberty is reached. At the same time the wall of the left side of the heart becomes thicker than the right, the length of the heart greater than the width, and the capacity of the ventricles exceed those of the auricles. The heart of the young child lies higher in the thorax than the heart of the adult, and as the child grows older it descends and

changes its general position till at the age of about twelve years, when it assumes the adult topography.

Physiologically the heart in early childhood becomes an independent working organ with every cell participating in the general functional activity and with certain specialized regions for specialized work. The sinus node, which is the remains of the obliterated sinus venosus, becomes the rhythmic center, and the His-Tawara system the conducting path. Every cardiac cell is ready to receive a stimulus, contract in response to it, and remain in a state of tonicity through the period of diastole. The circulation, however, is rapid and frequently unsteady because the cardiac nervous system which is made up of the autonomic and the sympathetic divisions is not in full and orderly control till late in childhood. The intracardiac pressure gradually increases with increased cardiac structure and function.

From this short outline of the anatomy and physiology of the heart during the three developmental stages of antinatal, natal, and postnatal life it is evident that the heart is constantly undergoing various anatomic and physiologic changes. It starts out as a primitive circulatory organ, but following the trail of evolution it is completed as a four-chambered heart. Originally made on a plan to serve a fetal circulation, it is quite suddenly called upon to change its form and function to accommodate itself to the new requirements of infancy. With the growth of the child the heart is constantly adapting itself to the ever-changing conditions. It is essentially a myogenic mechanism and is only gradually taken under the control of the nervous system. The heart does not attain maturity in size, capacity, and orderly functions till about the age of puberty.

Under these constantly changing conditions it is not strange that the heart of the child should be subject to physiologic peculiarities as well as pathologic abnormalities. The physiologic disorders must be carefully distinguished from the pathologic disorders in the examination of the cardiac mechanism in children. The workings of the heart of the child should be distinguished from the workings of the heart of the adult, and the diagnosis and treatment of heart diseases in children must not be

based on the anatomy, physiology, or pathology of the mature heart. The normal or abnormal functions of the young heart should be considered on the basis of its own anatomic peculiarities, physiologic aberrations, and pathologic vibrations. The abnormalities may be congenital or acquired.

The child's thorax may be abnormal in the anteroposterior diameter, length, or symmetry, causing various cardiac displacements. The precordium may be bulging, the cardiac impulse diffused, and the blood-vessels of the neck strongly pulsating. The apex is usually in the fourth interspace outside of the nipple line, shifting with change of position. A thrill is occasionally transmitted to the palpating hand by an overacting undulating heart. The cardiac sounds are loud, of almost equal intensity and duration. Unevenness, roughness, or splitting of either cardiac sound is not infrequently heard. These anatomic malpositions and physiologic dysfunctions do not portend cardiac disease in early life.

Murmurs in children may be physiologically congenital, pathologically congenital, physiologically acquired, or pathologically acquired. Murmurs caused by such fetal remnants as a patent ductus arteriosus or foramen ovale may be considered as physiologically congenital. They are not the result of any structural errors or pathologic processes and frequently disappear during childhood. When not complicated by any other cardiac anomaly they will cause little dynamic circulatory disturbance. All other congenital murmurs are pathologic.

To the group of physiologically acquired murmurs belong the so-called functional or accidental murmurs. They are common in children and cause no cardiac disorders. As these murmurs are generally associated with hearts of diminished tonicity they should, more properly, be called myatonic murmurs. Pathologically acquired murmurs are the result of endocarditis and valvulitis. They occur in later childhood and are heard mostly in the left side of the heart.

Physiologic derangements of rhythmicity, irritability, conductivity, contractility, or tonicity are quite common in children. This is mainly due to the fact that the child's heart is not under

the full control of its nervous system. A knowledge of these functional peculiarities in early life is of paramount importance in the diagnosis of the so-called cardiac child.

The sinus node, which sets the pace and regulates the rhythm of the heart, is normally under the guidance of the vagus nerve. Imperfect vagus inhibition and control results in the rapid rate and unsteady rhythm of the young heart. Sinus arrhythmia may be transient, more marked during sleep, changes with the respiratory phases, and disappears on rapid breathing or exercise. Atropin has but little pharmacologic action on the vagus nerve of the child's heart. Extrasystoles occasionally occur in children as a result of a hyperirritability of the cardiac syncytium or an over-excitability of the sympathetic cardiac nerve or because of cardio-toxicosis. Heart-block in children may be of functional origin due to an unusual blocking along the nerve-fibers which are embedded in the His-Tawara conducting path, preventing impulses coming from the sinus node to pass over to the ventricles. Irregular and wavy cardiac contractions and deficient cardiac tonicity are not uncommon in children. They cause reduplications of the cardiac sounds or unusual vibratory murmurs which have no pathologic significance. Pathologic arrhythmias due to poisonous substances acting on the myocardium or its nerve supply may occur in children. They should be carefully distinguished from the physiologic disorders.

The pulse rate, which is an index of the rate of impulse initiation in the sinus node, is more rapid in children than in the adult. The radial pulse should be compared with the apex-beat in order to detect any pulse deficit. Immediately after birth the heart rate is very rapid. There is a gradual slowing of the pulse rate until the infant is one year old, when it is about 120 per minute. At five years of age the rate is about 100 per minute. At ten years, 90, and at fifteen years, 80 per minute. The pulse rate, however, varies in different children of the same age, weight, and height.

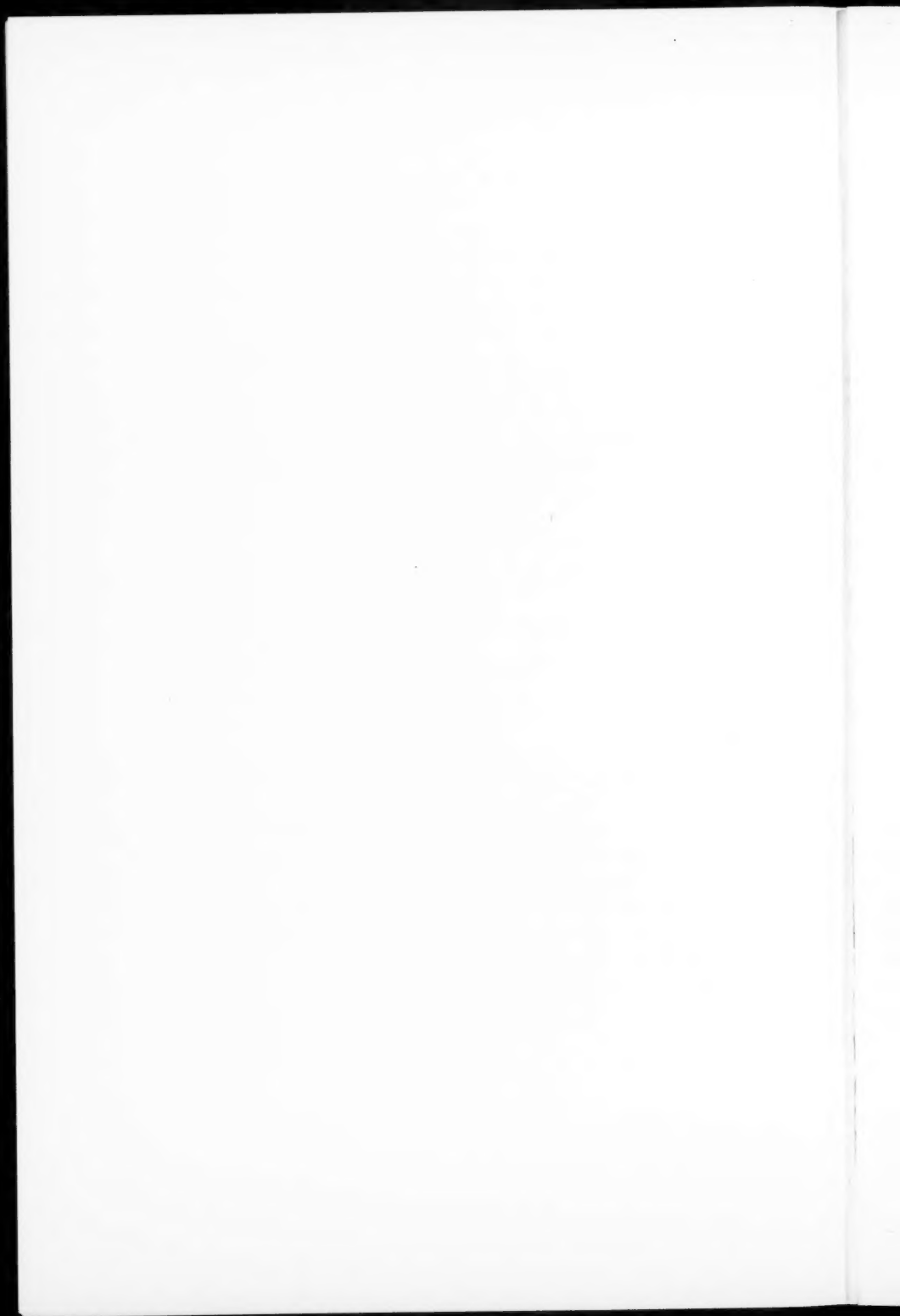
In order to maintain the fetal circulation the right intracardiac pressure must be greater than the left. After birth the left intracardiac pressure becomes greater than the right. The

cardiovascular blood-pressure gradually increases during childhood. As the child grows older and the pulse rate diminishes, the ventricles act more vigorously and the arteries are better filled with blood. The systolic pressure increases and the pulse pressure goes up according to the laws of dynamics. The systolic pressure rises from 75 to 90 during infancy, from 90 to 100 during childhood, and from 100 to 120 during adolescence. The diastolic pressure changes but little and the pulse pressure varies with the systolic. The pulmonary second sound gradually diminishes and the aortic second sound increases.

Electrocardiographic studies on the heart of the child have given conflicting results, but it has been definitely proved that during the first three months of life there is a right ventricular preponderance. After that the normal electrocardiogram indicates a gradual approach to the adult type of a left ventricular complex. This is in conformity with the gradual increase in thickness of the left ventricle during later infancy and childhood. Pathologic conditions may reverse the ventricular preponderance.

Summary.—Before the heart becomes a well-adapted and efficient mechanism it goes through three evolutionary periods—fetal, infantile, and childhood—each characterized by special circulatory requirements and by a gradual improvement in structure and function. As a result of the various anatomic and physiologic changes during the formative period, the many mechanical devices, inlets, and outlets, the heart is subject to maladjustments and dynamic disorders. The peculiar cardiac histogenesis, its incessant work, its contained mass of circulating fluid, make it susceptible to pathologic processes. Since murmurs are the result of obstructions, deviations, and detours in the course of the blood-stream, the unevenness of the inner surface of the ventricles, the guarding valves, the changes in the bed of the stream, from chamber to chamber, and from the heart to the blood-vessels, make the heart an ideal mechanism for murmurs. That every normal heart does not murmur shows the marvelous adaptation of the heart to its mechanical demands. Perhaps with finer instruments in

acoustics every heart may be found to be murmuring. With our present conception of murmurs their pathologic significance is in direct ratio to the pathology of the heart that is producing them, and for their clinical evaluation, subjective symptoms are worth more than objective signs. Cardiac disorders in early life may be congenital or acquired, pathologic or physiologic. A proper diagnosis is essential to the welfare of the child.



CLINIC OF DR. I. STRAUSS

PRESENTED AT CLINICAL CONFERENCE, MT. SINAI HOSPITAL

I. CASE OF CEREBRAL NEOPLASM

I AM showing this patient because he had a cerebral neoplasm, and I won't keep him long. I will show you how perfect he is, and then, afterward, I will describe the case for you.

DR. STRAUSS (to the patient): Get up and walk; go ahead, faster—come back. Good! Put your arms up, now down at your side, bring them forward! Close your eyes and bring your feet together. Touch your nose with the right index-finger—with the left. Tell me, where were you in school before you were taken ill?

PATIENT: I was a freshman, at college.

DR. STRAUSS: What were you studying?

PATIENT: I was studying for the degree of B. S. S., Bachelor of Social Sciences.

DR. STRAUSS: What studies did you have?

PATIENT: Literature, English history, economics, and some minors.

DR. STRAUSS: Have you any headache or anything wrong with you now at all? You feel perfectly well, don't you?

PATIENT: Yes, strong.

DR. STRAUSS (to the audience): You will see, here, the line of the osteoplastic flap. You can see that when his hair grows there will be nothing visible in the way of the scar. The patient's one worry is that his hair will not grow, but you can see that it is coming back and that the scar will be invisible probably in five years to come even to one looking for it.

QUESTION: Is there a decompression?

DR. STRAUSS: There is a decompression in the very lower angle which was done for a purpose at the operation. The de-

compression is very small and was part of the operative technic necessary in a case of this kind. (Exit patient.)

The patient has gone now, and so I may tell you his history. This boy is sixteen years of age. He was admitted to this hospital about six weeks ago. Four weeks previous to that time he was taken with severe headache and vomiting. There was slight rigidity of the neck, temperature 100.4° F. Examination showed that a right Babinski was present. There was a little flatness of the right face. He complained very severely of headache. A lumbar puncture was done and there was a marked increase of the spinal fluid. Following the puncture he was relieved. He went along then for a couple of days, when his headaches became severe again. A lumbar puncture was again performed with the removal of a great deal of fluid, after which he was again relieved.

Shortly after this he was brought into the hospital. Just before he came in bilateral papillo-edema was seen, not being at the time of very high degree. It is very interesting to note that just three days prior to admission to the hospital he became more or less stuporous, and at that time if you examined him you found that he was unable to read, could utter only a few words, was unable to carry out a command, and if you asked him to put his finger to his right ear he did not know what you meant—a form of apraxia. The right facial weakness became more marked. Babinski appeared on the left foot. He began to vomit. A lumbar puncture was again performed, and following this, on the next day, all symptoms disappeared. The ataxia, apraxia, agraphia, and alexia disappeared. He was brought into the hospital with slight rigidity of the neck, bilateral papillo-edema. The diagnosis of cerebral neoplasm was made, and because of the right facial weakness and the fact that he had had certain symptoms of alexia and agraphia, pointing to the left temporo-sphenoidal lobe, the diagnosis was made of a neoplasm probably in that region. In order to be certain a ventriculogram was made and the needle was inserted into the right occipital region. The needle was passed forward and the operator obtained about 60 c.c. of deep amber colored fluid which clotted immediately after

withdrawal. This was indication at once of the fact that the operator was in a cyst, so that from that point of view the diagnosis was absolutely certain. The assumption of tumor on the left side was ruled out by the obtaining of this fluid by the operator, which showed positively that he was in a cyst. Here is the lateral x-ray (Fig. 135) which is of the right ventricle. That is, it was supposed to be the right ventricle. Posteriorly you



Fig. 135.

can see the trephine opening. Air was injected into this (supposedly the right ventricle), but if you will look at the x-ray carefully you will see that apparently the anterior horn of the ventricle comes down to the frontal plate. This could not be if it was the anterior horn of the ventricle. Furthermore, down to that point the supposed ventricle is blocked by a mass coming up in a triangular shape, and the mass is bounded posteriorly by the supposed posterior horn. This latter proved to be part of the cyst surrounding the tumor, and the mass is the tumor. This cyst

surrounding the tumor was filled with air. The operator wasn't in the ventricle. The left plate will show how we knew this (Fig. 136).

What you see in this plate might have been interpreted, and, indeed, was considered by some to be the anterior horn of the ventricle. However, for an anterior horn of the ventricle it is a very markedly dilated one, and, in fact, the lower outline is too



Fig. 136.

round for that, and too sharp here. When you look at the picture you see that air has come over here laterally, but there can be no connection laterally by any such passage as that, so that here, again, we were not in the lateral ventricle, but in the cyst, and this mass here is the tumor covered over by a layer of air where the cyst is closely adherent to the tumor. Furthermore, you can see places if you study this plate where there were adhesions in the wall of the cyst.

This is the right temporal sphenoidal lobe below the middle cerebral vessel. It was cut right off, the base being the part that

was in life attached to the parietal lobe, running right back toward the occipital lobe. The tumor came to the surface on the inferior surface of this temporosphenoidal lobe.

This is the tumor, and the tumor surrounded by a cystic wall (Fig. 137). The tumor was encapsulated, sharply circumscribed, surrounded by the cyst. The wall of this cyst may be seen on

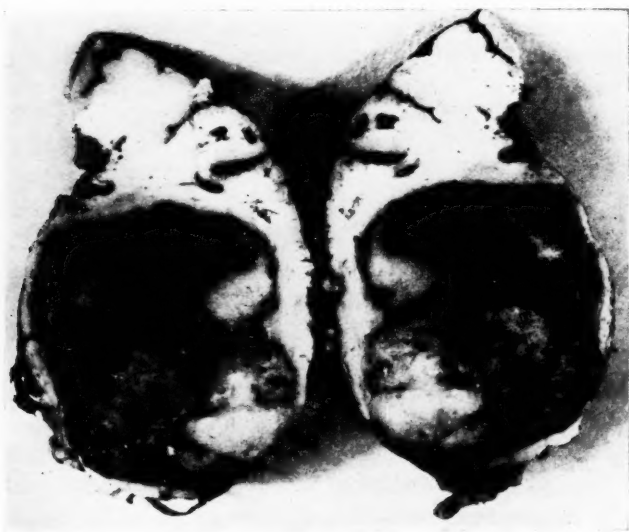
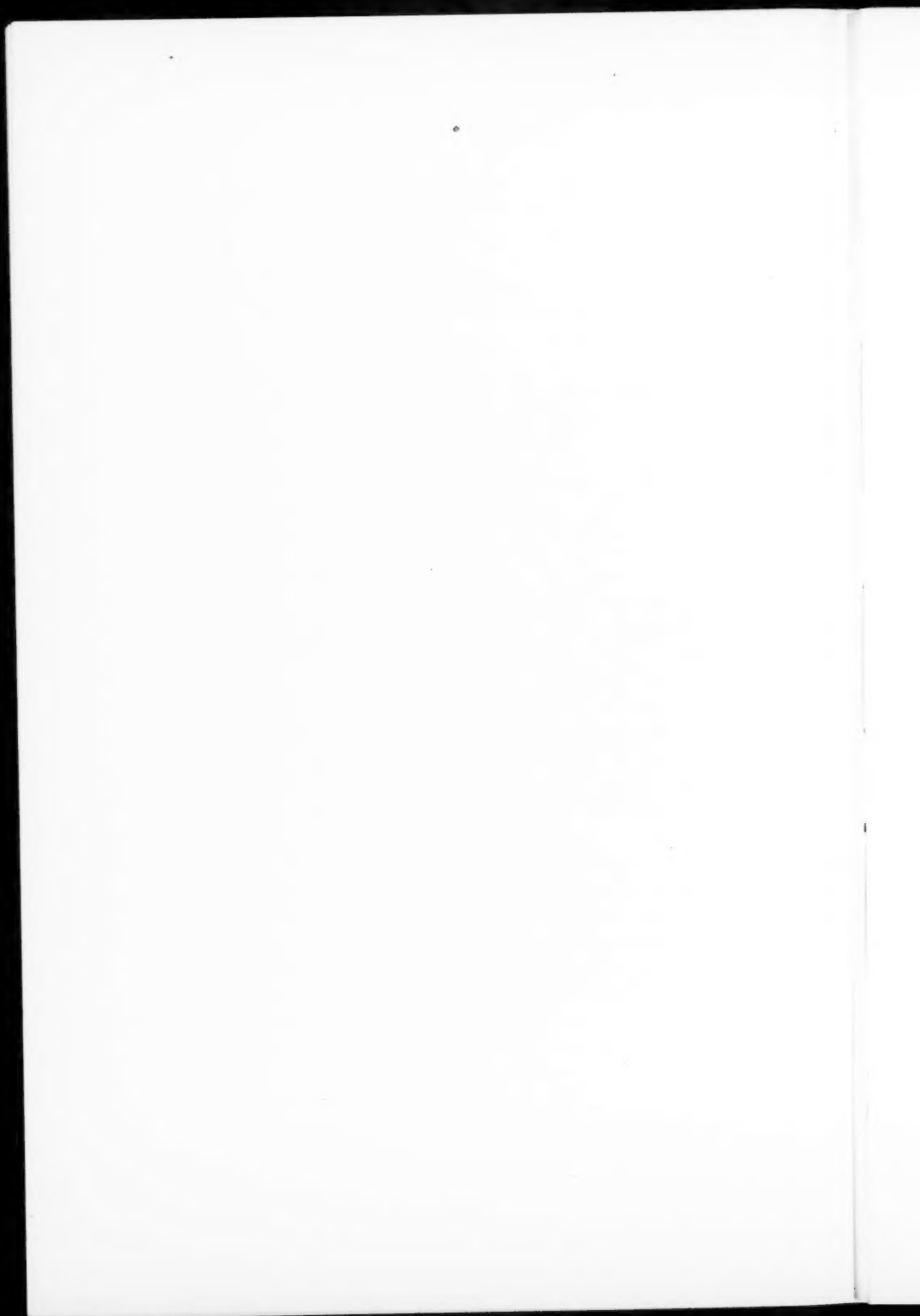


Fig. 137.

this photograph. It was into the cyst wall that the air was injected, and it was this large tumor mass that presented there. Now, then, all that this boy shows, as I have demonstrated, is the remains of a left hemianopia which he developed soon after he left the hospital. It is the only symptom he has. He is entirely well and has recovered in every respect. This left hemianopia will remain, of course, because the tumor pressed long enough on the optic radiation to destroy it, and it will probably never be restored.



II. CASE OF SARCOMA OF THE VERTEBRÆ WITH PARAPLEGIA IMPROVED BY DEEP x-RAY THERAPY

THIS patient has come to New York from Jersey City. I want you to see him walk.

DR. STRAUSS (to the patient): Lift both feet. How are you feeling?

PATIENT: Very well.

DR. STRAUSS: Can you pass your urine all right?

PATIENT: Yes.

DR. STRAUSS: Stomach?

PATIENT: Not so good.

DR. STRAUSS (to the audience): That means constipation. He complains of a little drawing sensation in his feet.

His history is as follows: He is fifty-three years of age now, and was admitted to the service September 22, 1925. This was his complaint—that for nine months he had had pain in both sacro-iliac regions, particularly the left. He had not been to an orthopedist. The pain began nine months before admission, but he had been treated at another hospital, where an x-ray of his spine was negative, where his chemistry (presumably blood chemistry) was negative, where his pyelogram blood and spinal fluid were negative, and where the diagnosis of chronic osteoarthritis was made. For two weeks he was given treatment by baking and some sort of injections that may have been epidural, so that he was able to walk. But after two or three weeks had elapsed he had a relapse. His pain returned in increasing severity; when he walked he was weak in the legs; and he began to lose control of his sphincters, so that when he came here to the hospital he presented the picture of paraparesis. His knee-jerks were diminished, he had marked tenderness—rather acute in fact—in the spinal region. At the same time below the level of the twelfth dorsal segment there were indications of diminished sensibility, and we suspected at once that he had a neoplasm which we

thought probably was a neoplasm in the spine. We did a lumbar puncture which showed a positive xanthochromic fluid and a positive Queckinstadt. We were rather reluctant to operate on him for the suspected tumor of the spinal column for fear it might be a secondary growth, and although I felt it might be a sarcoma of the bone I decided that he deserved a laminectomy. Before this was performed an x-ray was taken here and the x-ray finding was negative. They made the diagnosis of a chronic osteo-arthritic process. When he was operated on by Doctor Neuhoof it was found that he had a tumor affecting the arches of the seventh, eighth, ninth, tenth, and eleventh dorsal vertebræ. This tumor was found not only in the arches, but was, in fact, infiltrating the soft tissue, had come down to the dura, and also filled the extradural space, so that the surgeon recognized at once that we were dealing with a malignant growth, probably sarcoma. The tissue was sent to the laboratory and the diagnosis came back sarcoma. I will let Doctor Aschner tell you the type of tumor later. The patient was then sutured and turned over to the x-Ray Department for deep x-ray therapy. He was then absolutely paralyzed and could not control his bladder. From September 26th to October 30th he received eight deep x-ray treatments. He has been examined repeatedly since that time by members of the staff, and his Babinski and paralytic phenomena have gone, his sensibility has returned, he can walk, though slightly spastic, of course; his bladder control has returned, and we consider him probably a cured case of neoplastic sarcoma of the vertebræ, although he may have metastatic growth elsewhere.

III. LIPIODOL INJECTION FOR THE LOCALIZATION OF SPINAL CORD TUMORS AND OTHER LESIONS

I SUPPOSE most of you are familiar with the use of lipiodol. It is an oil preparation containing iodine which on the x-ray gives a dense shadow. We have used it thus far in various ways in the lungs for the diagnosis of the anatomy of the bronchial tube, etc., and we use it in the spinal column to aid us in the localization of spinal cord lesions. We introduce about 2 c.c. in the upper part of the vertebral column, in the cisterna magna, the routine which Ayer, of Boston, has demonstrated for various purposes. The substance is heavy and, therefore, sinks down into the vertebral canal.

Referring to the pictures, I will tell you about this case. This is a case of transverse myelitis, the bed case (negro) which Doctor Rabiner presented earlier.

We were certain that this man had no tumor of the spinal cord. However, it was a question of accuracy of the diagnosis, and so lipiodol was introduced in the way described. In a short time the lipiodol had come down to the sacral region just above the coccyx, where it is today. It will probably be there for sixteen months or longer. In only 1 or 2 cases has it been known to cause any irritative symptoms because of its long presence there. It may cause adhesions, and occasionally some cases suffer a little pain from irritation of the caudal nerve-roots, but irritative disturbances of this kind have been very rare and it has been used in a great many cases. This patient does not know that he has it, and if he is x-rayed out of the hospital and some radiographer outside sees it, he will probably tell the patient he has a bullet there. The x-ray of this case was negative for constriction of the cord, as we thought.

The next case is a colored woman whose disease, we felt, had gone back to childhood, and we felt it was a disease in the cord and deformity in the vertebræ. You will see the lipiodol

introduced above the cervical region, and that it has gone down, running into the lower part of the canal, showing no constriction whatever in the extra cord region. She, again, has had no symptoms from this, and the lipiodol is not annoying her.

The next case is a case where we diagnosed a lesion in the region of the first lumbar and twelfth dorsal vertebræ. This patient had presented symptoms of a lesion in that region, had a great deal of pain along the distribution of the first, second, and third lumbar roots, had atrophy of the leg, and sensory disturbances. We suspected that undoubtedly he had an extramedullary lesion of the cord. He had been under observation for some time in Bellevue Hospital, where they told him he had sciatica, and had given him injections without result. We did a Queckinstadt on him and obtained evidence of a partial block. We localized the tumor in this region, and tried the lipiodol injection. You will see that the lipiodol is arrested between the first lumbar and the twelfth dorsal vertebræ. Had we wished we could have injected lipiodol in this region between the second and third lumbar, turning the patient with the head down, and we would have found the lipiodol coming up to the point, so that in this way we could have localized our tumor both from below and above, and could have told the surgeon just where to find it. At operation no tumor presented, but there was an inflammatory process of the pia-arachnoid which had blocked the spinal canal, causing all the pain, producing the irritation of the spinal root nerves, and causing all the symptoms. Since the laminectomy he has been absolutely free from pain, his motility is good, and he has recovered from the atrophy of the leg, his reflexes are returning, and, to all intents and purposes, he is getting along very well. The cause of this inflammatory process we do not know. Here the lipiodol confirmed our diagnosis of obstruction, although it turned out not to be a tumor.

The next picture is the same case in which, subsequently, the lipiodol finally reached past the block, showing that the obstruction was not complete. Had my staff seen this subsequent plate they would have been able to say that this could not be a complete obstruction. They would have suspected that it was not a

tumor in the canal, but something else. This second picture would not have prevented them from operating, but would have thrown more light on the nature of the obstruction.

The next picture (Fig. 138) is a case in which we diagnosed, again, a complete block. This boy had a complete spastic hyperplasia which he had had for a long time, and while we had localized, from our clinical findings, the approximate locality of the obstruction, we thought we would try lipiodol. It brought out a very interesting condition. You will see the lipiodol, rather

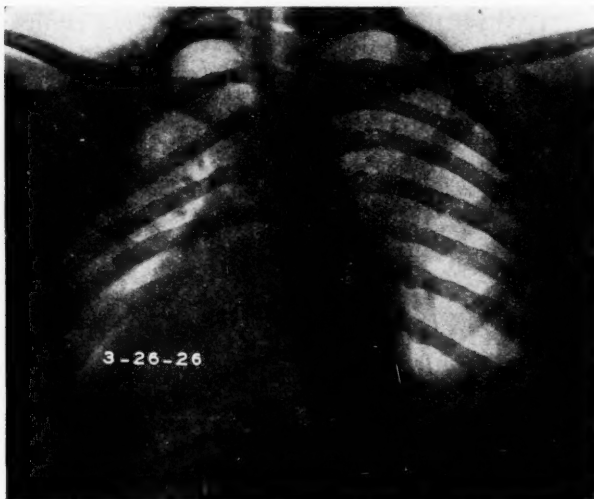


Fig. 138.

straight across, coming down in a narrow sheath—not the picture you see usually when a tumor is present, and we assumed, therefore, that while this patient might have a tumor the obstruction must be of two or three vertebræ and that it was compressing the cord. It was at the same time leaving some space into which this lipiodol could sink. The patient was operated on and it was found that he had a very thick dura. He had pachymeningitis, suppurative chronica, a chronic inflammatory process of the dura restricting the cord. The surgeon in this case did not think it

wise to open the dura, and I think he was right because the symptoms had continued so long that he believed he might have developed a meningitis. When we looked at the x-ray subsequently we found some signs of disease of the vertebræ which bears out the belief that in doing a lipiodol injection we ought to examine and x-ray the vertebræ first. I have presented these cases, however, to show you how lipiodol can aid in the diagnosis of spinal cord condition.

